UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

In re AVEO Pharmaceuticals, Inc. Securities Litigation	Civ. A. No. 1:13-cv-11157-DJC
	CLASS ACTION
This document relates to: All Actions	**CONSOLIDATED AMENDED COMPLAINT FOR VIOLATIONS OF FEDERAL SECURITIES LAWS**
	DEMAND FOR JURY TRIAL

Lead Plaintiffs Robert Levine and William Windham ("Plaintiffs"), individually and on behalf of all other persons similarly situated, by their undersigned attorneys, for their complaint against Defendants, allege the following based upon personal knowledge as to themselves and their own acts, and information and belief as to all other matters, based upon, inter alia, the investigation conducted by and through their attorneys, which included, among other things, a review of the Defendants' public documents, conference calls, television appearances and announcements made by Defendants, United States Securities and Exchange Commission ("SEC") filings, wire and press releases published by and regarding AVEO Pharmaceuticals Inc. ("AVEO" or the "Company"), briefing documents and transcripts published by the United States Food and Drug Administration ("FDA"), analysts' reports and advisories about the Company, and information readily obtainable on the Internet.

NATURE OF THE ACTION

1. This is a federal securities class action on behalf of a class consisting of all persons other than defendants who purchased AVEO common stock between January 3, 2012 and May 1, 2013, both dates inclusive (the "Class Period"), seeking to recover damages caused

by Defendants' violations of the federal securities laws and to pursue remedies under the Securities Exchange Act of 1934 (the "Exchange Act").

2. AVEO is a biopharmaceutical company focused on discovering, developing, and commercializing cancer therapies. AVEO's lead product is tivozanib (trade name Tivopath), an oral inhibitor of the vascular endothelial growth factor receptors ("VEGF inhibitor") that the Company aims to commercialize as a targeted treatment for advanced renal cell carcinoma, the most prevalent form of kidney cancer. AVEO has no other advanced stage products in its development pipeline, and is valued by the market based primarily on the prospects for tivozanib.

3. In the United States, the FDA is prohibited from approving any drug not demonstrated by the drug's sponsor (here, AVEO) to be safe and effective. The requirement for establishing both safety and efficacy takes on particular importance for cancer drugs like tivozanib, because they are generally toxic and can be lethal to patients even if effective in stopping the progress of a disease. Accordingly, trials for drugs intended to treat cancer generally measure both *overall survival*, which measures the length of time from the start of treatment in which the patient remains alive, and *progression-free survival*, the length of time after the start of treatment in which the patient remains alive and the disease, as assessed by study researchers, has not worsened.[1]

4. Overall survival is considered to be the "gold standard" for clinical trials. Overall survival is an objective, clinical endpoint. However, establishing advantage in overall survival generally requires a larger patient population and takes much longer to assess, because it can

[1] *See, generally*, dictionary published by National Cancer Institute for definitions of these and other terms, available at http://cancer.gov/dictionary.

only be measured when a patient dies, even if the patient has completed treatment. For these reasons, studies focusing on overall survival tend to be significantly longer and more expensive than those focusing on surrogate endpoints like progression-free survival. Another disadvantage of overall survival is that it can be confounded by subsequent treatments.

5. Progression-free survival, on the other hand, is often favored by drug companies because it can allow for smaller and cheaper trials. For progression-free survival in renal carcinoma, the progression of the disease is assessed at regular intervals using radiologic scans. A patient is considered to have achieved "progression-free survival" if she remains alive and the radiologic scans demonstrate that the tumor has not grown more than a pre-specified amount. Approximately 92% of the progression-free survival results for the clinical trial at issue in this case were attributable to radiological tumor measurements, as opposed to the actual life or death of the patient.

6. Progression-free survival is considered a surrogate rather than a pure clinical endpoint, because tumor size is correlated with but not a direct measure of survival. As Derek Lowe, a journalist following the pharmaceutical industry, noted: "progression-free survival does not necessarily mean 'survival', not in the sense that cancer patients and their relatives really care about. Dying in the same amount of time, albeit with redistributed tumor tissue, is not the endpoint that people are waiting for."[2] Another disadvantage of progression-free survival is that it relies on human judgment and assessment, and is therefore prone to bias, especially in open label studies, *i.e.*, studies in which researchers and patients know who receives the study drug and who receives the control or placebo drug.

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[2] Lowe, D., "Does AVEO's Tivozanib Work, Or Not?," Aug. 2, 2012, available at http://pipeline.corante.com/archives/2012/08/08/does_aveos_tivozanib_work_or_not.php.

7. Because it takes far less time and expense to sufficiently power a clinical trial focusing on progression-free survival than overall survival, the FDA has allowed progression-free survival to serve as a primary endpoint for Phase 3 trials of treatments for renal cell carcinoma. However, the FDA has routinely considered overall survival – the life and death of patients – as a crucial element for approval of renal cell carcinoma treatments, even where progression-free survival was the primary endpoint.

8. In December 2008 and May 2009, AVEO met with the FDA regarding the design of a Phase III trial assessing tivozanib as a first-line treatment for renal cell cancer. Those meetings included substantial discussion of the role of progression-free survival data and overall survival data in the regulatory approval process. During those meetings, the FDA concurred that "a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive may be considered for regulatory decision." The FDA acknowledged the difficulty in establishing statistical significance in overall survival, allowing that "statistically significant improvement…is not required for regulatory approval." However, the FDA expressly requested that the sponsor include in its trials a pre-specified plan for analyzing overall survival, and told AVEO that such analysis was "helpful in the regulatory decision making process." Thereafter, Defendants designed and conducted the Phase III trial, an open-label study that the Company called TIVO-1. Progression-free survival was the primary endpoint for the TIVO-1 study, and overall survival a crucial secondary endpoint. As is detailed herein, Defendants did not conduct the trial according to protocol or consistent with their discussions with the FDA. Instead, they introduced design defects and engaged in study misconduct that rendered the trial scientifically invalid.

9. Patients enrolled in TIVO-1 were randomized to one of two arms. The experimental arm received tivozanib. The control arm received sorafenib (trade name Nexavar), a first-generation targeted therapy that was approved by the FDA in 2005 for the treatment of renal cell carcinoma. At the time of the TIVO-1 trial, sorafenib had ceased being used as a first-line treatment for renal cell carcinoma by most oncologists in the United States, who shifted patients to superior second-generation targeted therapies like sutinib. Defendants introduced three design defects into the TIVO-1 study, the effects of which they concealed from investors throughout the Class Period.

10. First, Defendants confounded the study results by offering a crossover, or subsequent therapy, to one study arm without offering the same to the other study arm. This crossover was not included on either the preliminary or final protocols for the TIVO-1 trial, and was not discussed with the FDA. Under the crossover, patients randomized to the sorafenib (control) arm were given the opportunity to "cross over," or switch to tivozanib as a subsequent treatment, without cost. By contrast, patients randomized to the tivozanib arm were not offered any subsidized second-line treatment. Defendants introduced the one-way crossover as a perk to entice and maintain enrollment in the TIVO-1, so that patients randomized to receive sorafenib would not leave the trial.

11. As detailed herein, the FDA has warned, and Defendants at all relevant times understood, that such one-way crossovers could compromise the ability to assess overall survival. When a patient is crossed over to a subsequent therapy it is difficult and often impossible to determine whether that patient's survival benefit was attributable to the randomized therapy or the subsequent treatment.

12. Second, Defendants chose to enroll their test almost exclusively in Eastern Europe, where they knew second-line therapies were not commonly used for treatment of renal cell carcinoma. This exacerbated the design defect caused by the one-way crossover, because it ensured that patients randomized to the tivozanib arm were unlikely to receive any subsequent targeted therapy, whereas patients randomized to the sorafenib would receive a subsequent therapy – tivozanib – for free.

13. Third, while both study arms allowed for dose reductions if patients were experiencing adverse reactions, Defendants arranged for the dosages to be reduced at materially different rates. Dosage rates of the control drug, sorafenib, were cut by 50% when the dose was reduced (with the option for investigators to further halve the dosage), whereas rates of tivozanib were only reduced by 33% (with no option for further reduction). As a result, it was unclear whether patients in the sorafenib (control) arm who experienced disease progression after dose reduction did so because of the exaggerated dose reduction, or because there was a difference in the therapeutic effects of the compared drugs. This design defect compromised the progression-free survival results of the study.

14. In the Spring of 2012, AVEO requested a formal pre-New Drug Application ("NDA") meeting with the FDA. The request was granted and the meeting was held in May 2012. During the meeting, as Defendants would admit after the Class Period, "[t]he agency expressed a concern about the adverse trend in overall survival. Further discussion of these findings will be required at the time of filing, and if the application is filed, there will be a review issue that could affect approvability. The FDA recommended that the sponsor conduct a second adequately-powered randomized trial in a population comparable to that in the U.S." Although Defendants now concede that these damaging statements were memorialized in official meeting

minutes distributed to them, Defendants to date have declined to release those minutes to investors, and the FDA was prohibited by agency privacy regulations from even mentioning the minutes except in the context of an advisory committee meeting.

15. Only days later, Defendant Ronald DePinho appeared on investor news network CNBC. Defendant DePinho had co-founded AVEO over a decade earlier, with his wife Lynda Chin, and remained a director and major shareholder. Although DePinho knew that tivozanib patients were dying at a more rapid rate than control group patients, and almost certainly knew that the FDA had expressed concern to the Company regarding the higher death rate of tivozanib patients, he encouraged investors to bet on AVEO. He boasted to the national television audience that AVEO's had a "very effective drug that has a superior safety profile for renal cell cancer, a major unmet need." Between May 2012 and August 2012, Defendants (and AVEO corporate officers) Tuan Ha-Ngoc, William Slichenmyer, and David N. Johnston continued to hype AVEO's prospects at industry and investor conferences, and in press releases and SEC filings.

16. Each of Defendants' promotional statements, as is detailed and attributed herein, concealed the most important information that investors needed to know about AVEO and tivozanib:

- that design defects and study misconduct in the Phase 3 clinical trial for tivozanib were so severe that the results of the trial were uninterpretable and thus categorically unable to provide the evidence of efficacy or safety required by law before approval can be granted;
- that the FDA had expressed serious concerns regarding the adverse trend in overall survival;

- that the FDA had recommended a second adequately-powered randomized trial in a comparable population;
- that the FDA questioned whether an NDA should even be filed; and
- that the FDA had expressly indicated that the adverse trend in overall survival could affect approvability.

17. On August 2, 2012, AVEO admitted for the first time that the FDA had concerns about overall survival statistics, even though the FDA had communicated this information to AVEO months earlier. In reaction to the disclosure of this material adverse information, AVEO shares dropped from $13.30 to close at $9.75, a decline of nearly 27%, on very high volume.

18. Although the August 2, 2012 drop was severe, AVEO was able to buffer the decline by omitting the most important information that the FDA conveyed to it regarding overall survival. Defendants did not disclose that the agency had recommended a second adequately-powered trial in a comparable population, that the agency questioned whether the NDA should be filed at all, and that the agency had expressly warned that adverse overall survival trends could affect approvability.

19. The FDA scheduled an advisory committee meeting for consideration of tivozanib to take place on May 2, 2013. An advisory committee is a committee that the FDA convenes under the procedures established by the Federal Advisory Committee Act ("FACA"), 5 U.S.C. App. 2, and regulations promulgated thereunder, to provide the FDA with independent technical advice. Because FACA requires that advisory committee meetings be open to the public and advisory committee briefing documents be disclosed to the public, FDA advisory committees also provide a unique forum for the public to gain insight into FDA concerns about drug

applications that would otherwise remain silent. *See* FACA, http://www.acus.gov/research-projects/federal-advisory-committee-act.

20. On April 30, 2013, the FDA released its Oncologic Drugs Advisory Committee ("ODAC") briefing document (the "Briefing Document") that, among other matters, criticized the design and conduct of AVEO's only pivotal clinical trial and revealed that the FDA had asked AVEO a year earlier to conduct another clinical trial that was better designed and in a comparable patient population, but the Company had disregarded its advice. Specifically, the Briefing Document explained that "[a] pre-NDA meeting was held in May 2012. Here, the FDA expressed concern about the adverse trend in overall survival in the single Phase 3 trial ("TIVO-1") and recommended that the sponsor [AVEO] conduct a second adequately powered randomized trial in a population comparable to that in the US."

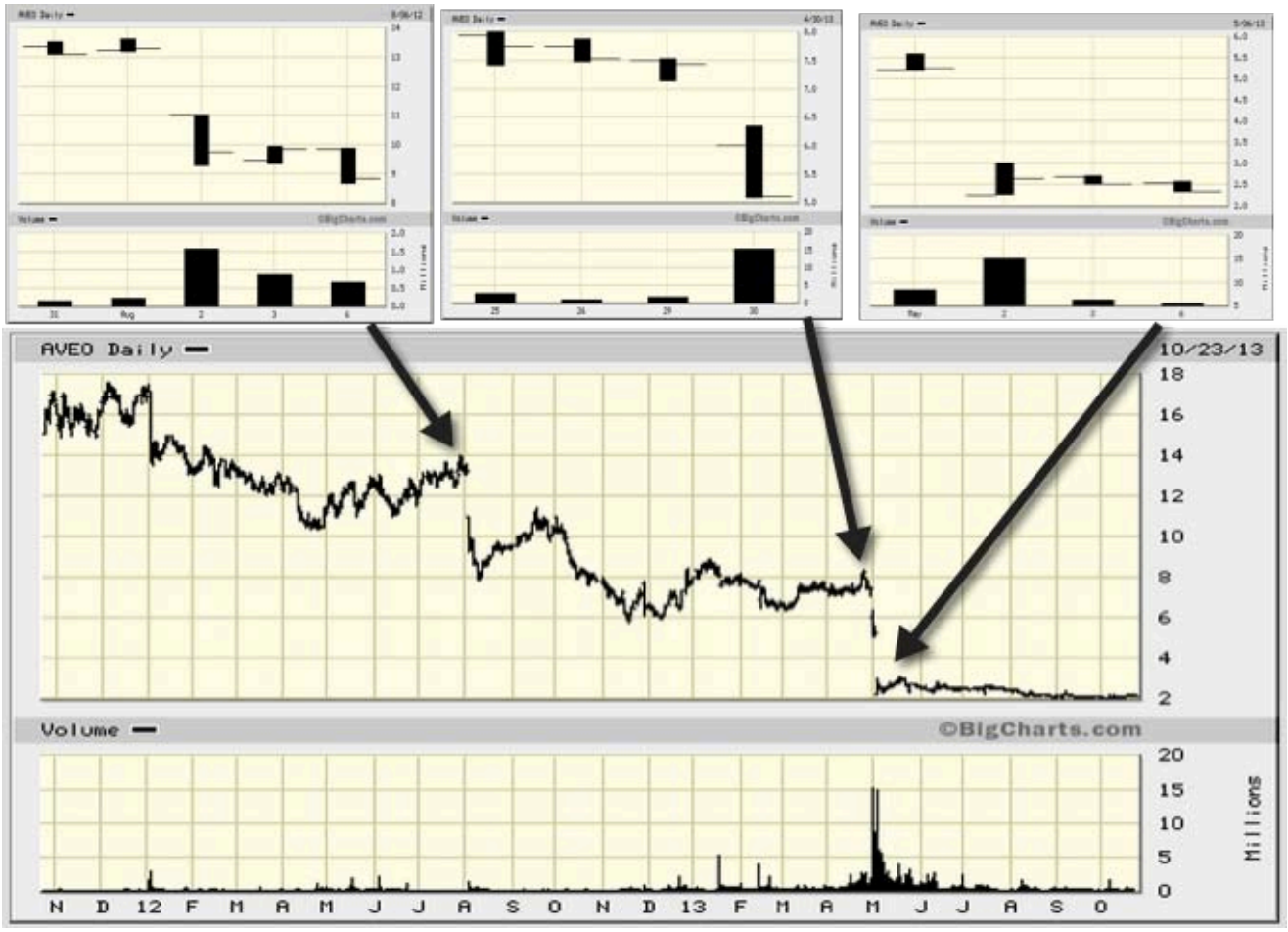
21. In response to the further revelations disclosed in the FDA's Briefing Document, AVEO shares fell $2.33 or 31.31% per share to close at $5.11 on April 30, 2013, on volume of over 15 million shares.

22. On May 2, 2013, the Company and the FDA made presentations to the ODAC panel regarding the new drug application of tivozanib. The FDA noted in its presentation that: (a) tivozanib actually increased potential risk of death by 25% compared to the control drug, sorafenib; (b) tivozanib therapy induced higher rates of hypertension, hemorrhage and dysphonia than sorafenib; (c) TIVO-1 had a flawed trial design; (d) TIVO-1 provided internally inconsistent trial results; (e) TIVO-1 provided uninterpretable overall survival results; and (f) TIVO-1 provided inconclusive risk-benefit assessment data.

23. On May 2, 2013, the ODAC voted by an overwhelming majority, 13 to 1, not to recommend approval of the tivozanib, because, "the application for investigational agent

tivozanib did not demonstrate a favorable benefit-to-risk evaluation for the treatment of advanced renal cell carcinoma (RCC) in an adequate and well-controlled trial."

24. When the stock, which was halted during the ODAC panel presentation, began to trade again, it dropped sharply as a result of the further disclosures made during the ODAC presentation. In the afternoon of May 2, 2013, AVEO shares declined $2.61 per share or nearly 50%, to close at $2.65 per share, on volume of over 15 million shares. The chart below demonstrates that each of the three partial disclosures identified herein (August 2, 2012; April 30, 2013; and May 2, 2013) was immediately followed by a substantial, high-volume decline in AVEO's common stock:



25. As a result of Defendants' wrongful acts and omissions, and the precipitous decline in the market value of the Company's securities, Plaintiff and other Class members have suffered significant damages.

JURISDICTION AND VENUE

26. The claims asserted herein arise under and pursuant to Sections l0(b) and 20(a) of the Exchange Act, 15 U.S.C. §§ 78j(b) and 78t(a), and Rule l0b-5 promulgated thereunder by the SEC, 17 C.F.R § 240.10b-5.

27. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1337, and Section 27 of the Exchange Act, 15 U.S.C. § 78aa.

28. Venue is proper in this District pursuant to Section 27 of the Exchange Act, and 28 U.S.C. § 1391(b). AVEO maintains its principal place of business in this District and many of the acts and practices complained of occurred in substantial part herein.

29. In connection with the acts alleged in this complaint, Defendants, directly or indirectly, used the means and instrumentalities of interstate commerce, including, but not limited to, the mails, interstate telephone communications, and the facilities of the national securities markets.

PARTIES

30. Plaintiff Robert Levine purchased AVEO common stock during the Class Period as set forth in the certification previously filed with this Court and was damaged as the result of Defendants' wrongdoing as alleged in this complaint.

31. Plaintiff William Windham purchased AVEO common stock during the Class Period as set forth in the certification previously filed with this Court and was damaged as the result of Defendants' wrongdoing as alleged in this complaint.

32. Defendant AVEO is a corporation organized under the laws of the state of Delaware, maintaining its principal place of business at 75 Sidney Street, Cambridge, MA 02139. AVEO's common stock trades on the NASDAQ Global Stock Market ("NASDAQ") under the ticker symbol "AVEO."

33. Defendant Tuan Ha-Ngoc ("Ha-Ngoc") was President, Chief Executive Officer, and Director of AVEO at all times relevant hereto.

34. Defendant David N. Johnston ("Johnston") was AVEO's Chief Financial Officer at all times relevant hereto.

35. Defendant William Slichenmyer ("Slichenmyer") was AVEO's Chief Medical Officer at all times relevant hereto.

36. Defendant Ronald DePinho ("DePinho") was a co-founder of AVEO and was a Director of the Company at all times relevant hereto. DePinho was referenced in AVEO's SEC filings as a "scientific founder" of the Company. Prior to the Class Period, DePinho also served as a member of AVEO's scientific advisory board. While DePinho relinquished that position for himself, DePinho's wife Lynda Chin remained on the scientific advisory board during the Class Period.

37. The defendants referenced above in ¶¶ 33-36 are referred to herein as the "Individual Defendants."

SUBSTANTIVE ALLEGATIONS

BACKGROUND

The FDA New Drug Approval Process

38. In the United States, pharmaceutical development and marketing is regulated by the FDA, an agency of the U.S. Department of Health and Human Services. The modern

regulatory regime was enacted in 1962, after Thalidomide, a sleeping pill, caused birth defects in thousands of babies. In reaction to this tragedy, Congress passed the Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act (the "FDCA") requiring that any company that wanted to market a pharmaceutical product in the United States (in industry parlance, a "sponsor") had to obtain prior approval from the FDA, and that the approval had to be based upon substantial scientific evidence demonstrating that the product was safe and effective for its intended use in humans.

39. The FDCA, as amended, requires the Commissioner of the FDA to refuse any drug application if:

- "he has insufficient information to determine whether such drug is safe for use under such conditions;" or
- "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."

21 U.S.C. § 355(d)(4)-(5).

40. The FDA is only permitted to consider clinical evidence to be "substantial," and thus satisfy the FDCA, if it:

> consist[s] of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C. § 355(d). Well-controlled clinical investigations measure the subject drug against a control group, which is provided either a placebo or another recognized drug for comparison.

Moreover, well-controlled clinical investigations generally are conducted in a "double-blinded" manner, meaning that the tests are designed so that the study participants and the investigators (as well as the sponsor and associated research organizations) do not know whether each participant has been provided the candidate drug or is a member of the control group. Double-blinding is intended to minimize test bias and error that can arise when the participant and/or investigator have knowledge of the assigned treatment.

41. The sponsor, not the FDA, is responsible for determining the design of clinical trials and the protocols for each trial. If a sponsor wants the FDA to agree to the sufficiency of a particular protocol, the sponsor may request a Special Protocol Assessment pursuant to 21 U.S.C. § 355(b)(5)(C). Under this provision, the FDA and sponsor meet to discuss the sponsor's proposed protocols, and reduce any agreements to writings that become part of the administrative record. Such agreements may not be changed except by mutual consent or under exceptional medical or scientific circumstances. *Id.* AVEO did not apply for, and did not receive, any Special Protocol Assessments in connection with the TIVO-1 trial of tivozanib.

42. Sponsors are also responsible for enrolling patients in clinical trials. Enrollment can be a lengthy and expensive part of a clinical trial, especially in a larger trial, a trial for a rare disease, or a trial in a field with other competing studies. Regardless of where patients are enrolled, a sponsor must ensure that the trial is conducted according to protocol, and must demonstrate benefit to the patient population for which approval is sought.

43. A sponsor generally conducts clinical trials in three phases. These phases, which are codified in FDA regulations, are as follows:

- Phase I. Phase I studies "are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness."
- Phase II. Phase II studies are "typically well controlled" studies "conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug."
- Phase III. Phase III studies are expanded studies "performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects."

21 C.F.R. § 312.21.

44. When a sponsor believes it has conducted sufficient well-controlled clinical trials, and believes that those trials demonstrate substantial evidence of efficacy and safety consistent with the FDCA, the sponsor may prepare and file an NDA with the FDA seeking approval to the market the subject drug in a specific dose for the treatment of a specific condition or "indication." The NDA must also specify how the drug will be manufactured, packaged and labeled. The FDA can only grant approval when presented with scientific evidence meeting the requisite statutory criteria.

45. Within sixty (60) days of receiving an NDA, the FDA will accept the NDA for filing if it believes the NDA is sufficiently complete to permit a substantive review of the

information contained within the NDA. The acceptance of an NDA for filing is not a determination of the substantive merits of the NDA, but rather a threshold determination of whether there is enough data to conduct a substantive examination. If the FDA determines that there is a facial problem preventing a meaningful substantive examination – for example, if the NDA is missing paperwork, fails to include data in the proper format, or suffers from other facial errors that make review impossible – the FDA may refuse to file the NDA.

46. The filing of an NDA triggers review deadlines specified in the Prescription Drug User Fee Act ("PDUFA"), enacted in 1992 and reauthorized by amendment every five years thereafter. Under the PDUFA, the FDA is generally required to respond to the NDA within six months. The date by which the FDA must issue its response is frequently referred to as a drug's "PDUFA date."

47. An NDA accepted for filing is reviewed for substance by the FDA's Center for Drug Evaluation & Research ("CDER"). Prior to the PDUFA date, CDER may (or may not) convene an advisory committee to provide it with technical advice, enhance its decision-making process, and provide a forum for public discussion of controversial issues.

48. Where an advisory committee is convened, the sponsor and the FDA staff will each provide the advisory committee briefing documents and make presentations to the advisory committee. After receiving the submissions of both the sponsor and the FDA, and hearing their respective presentations, the advisory committee will discuss the safety and efficacy of the drug candidate and provide the FDA with a nonbinding vote on specific questions regarding safety and efficacy, and whether approval is warranted based upon the evidence of safety and efficacy provided by the sponsor.

49. Critically, an advisory committee is the only forum in which the public can legally be advised by the FDA of the FDA's position and the FDA's interactions with the sponsor regarding the drug candidate. Except in advisory committee briefing documents and during the advisory committee hearing, FDA secrecy regulations strictly prohibit the agency from disclosing information regarding pending NDAs. As a result, without an advisory committee, the FDA may not publicly refute a sponsor's misrepresentations regarding clinical trials, protocols, or the sponsor's interactions with the FDA, no matter how false or misleading those statements may be. *See* 21 C.F.R. § 314.430.

AVEO compromises pivotal TIVO-1 clinical trial with off-protocol design flaws

50. AVEO is a biopharmaceutical company focused on discovering, developing, and commercializing cancer therapeutics. The Company's lead product candidate, tivozanib (trade name Tivopath) is an oral inhibitor of the vascular endothelial growth factor ("VEGF") receptors. VEGF is a signal protein produced by cells that stimulates blood vessel creation. When overexpressed, VEGF can contribute to the growth of cancerous tumors, because solid cancers cannot grow beyond a limited size without an adequate blood supply.

51. Drugs which inhibit VEGF receptors have been approved as targeted treatments for renal cell carcinoma since 2005, replacing cytokine therapy such as interferon-alpha and interleukin-2, and systemic therapies such as chemotherapy. Approved anti-VEGF drugs for the treatment of renal cell carcinoma include sorafenib, sutinib, and pazopanib, among others. AVEO sought to gain approval and commercialize tivozanib as a competitor to these established first-line therapies for the treatment of renal cell carcinoma.

52. Defendants, who claimed in their representations to investors to be familiar with and able to speak competently regarding the pivotal clinical trials supporting the approval of

other anti-VEGF drugs, knew that no anti-VEGF drug had ever been approved where it showed a higher risk of death, *i.e.,* worse overall survival.

53. In December 2008 and May 2009, AVEO met with the FDA regarding the design of a pivotal clinical trial for tivozanib. During those meetings, the FDA expressly requested that the Company analyze overall survival of study participants in addition to progression-free survival. AVEO did not discuss with the FDA a crossover of study participants from one therapy to another in either of those meetings. AVEO has to date not disclosed which AVEO officers and advisors participated in the December 2008 and May 2009 meetings, and continues to conceal from investors the meeting minutes that would reflect that information. However, it is expected that, at a minimum, Defendants Ha-Ngoc and Slichenmyer participated in these meetings because the participation of the Chief Executive Officer and Chief Medical Officer in crucial meetings with the FDA would be standard practice for a company of AVEO's size, especially where as here such meetings related to a flagship drug candidate. Moreover, it is a standard practice at development-stage pharmaceutical companies of the size of AVEO to immediately debrief top-level executives, diectors, and regulatory consultants following key FDA meetings, and to record the Company's view of the contents of such meetings into corporate minutes or a debriefing memorandum.

54. Following the December 2008 and May 2009 meetings, the Company specified a protocol for a Phase III clinical trial known as Study 301 and referred to by the Company as TIVO-1. According to the protocol, TIVO-1 was a randomized, open-label comparison trial where the experimental arm was provided tivozanib and the control arm provided sorafenib, an approved treatment for renal cell carcinoma. The protocol for TIVO-1 designated a statistically-significant improvement in progression-free survival as the primary endpoint, and a comparison

of overall survival as a secondary endpoint. As the FDA explained in the ODAC advisory committee panel, the pre-specified statistical analysis plan for TIVO-1 indicated a hierarchical analysis of secondary endpoints under which the overall survival comparison was the most important, and analysis of other secondary endpoints not to be undertaken unless an overall survival benefit was achieved.

55. The TIVO-1 protocol stated that participants would be enrolled in approximately 90-100 sites worldwide and stratified by geography into three major geographic groups: North American/Western Europe, Central/Eastern Europe, and the "Rest of the World." The pre-specification of geographic stratification reflected Defendants' understanding, at all relevant times, that treatment for renal cell carcinoma varied across geographies. Defendants could easily have ensured that the TIVO-1 was enrolled globally as specified instead of clustered in Eastern and Central Europe by capping enrollment by site, or by opening additional sites in the United States and/or Western Europe, but chose not to because to do so could delay the trial and make it more expensive.

56. The TIVO-1 protocol did not provide for (or even mention) the crossover of study participants from one therapy to another. Instead, after the specification of protocol for TIVO-1 and prior to trial initiation, AVEO created a separate trial it called Study 902 for the sole purpose of providing tivozanib free of charge to participants in TIVO-1 who were randomized to the sorafenib (control) arm and experienced disease progression.

57. AVEO began enrolling participants for TIVO-1 in or around February 2010 and completed enrollment in or around August 2010. Contrary to protocol specifications calling for a broad worldwide trial stratified across geographies, AVEO enrolled approximately 88% of TIVO-1 participants in Central and Eastern Europe, where enrollment and testing were cheaper.

Because TIVO-1 was an open label study, data was not blinded from the sponsor and the sponsor was able to monitor the progress of the trial at all relevant times.

58. In 2011, AVEO entered into a partnership with Astellas Pharma ("Astellas"), a global pharmaceutical company headquartered in Japan, for the development and marketing of tivozanib. Under the agreement, Astellas made a significant cash contribution to AVEO, and agreed to split certain development costs for tivozanib. In exchange, Astellas received a 50% interest in tivozanib. The agreement provided that AVEO would lead efforts to gain approval and market the drug in the United States, while Astellas would lead commercialization efforts in Europe.

59. By early January 2012, the start of the Class Period, AVEO had gathered nearly sixteen months of data in TIVO-1 and knew that what initially began as an adverse trend in overall survival had not only continued but worsened. It was clear by this time that patients randomized to the tivozanib arm were dying more frequently than those randomized to the sorafenib (control) arm.

MATERIALLY FALSE AND MISLEADING STATEMENTS MADE DURING THE CLASS PERIOD

60. The Class Period begins on January 3, 2012, when the Company issued a press release announcing positive preliminary results from the Phase 3 TIVO-1 trial but omitting material adverse information regarding design defects so severe they rendered the results of that trial uninterpretable. Specifically, the press release stated:

> [T]hat tivozanib demonstrated superiority over sorafenib in the primary endpoint of progression-free survival (PFS) in TIVO-1, a global, randomized Phase 3 clinical trial evaluating the efficacy and safety of investigational drug tivozanib compared to sorafenib in 517 patients with advanced renal cell carcinoma (RCC). TIVO-1 is the first registration study in first-line RCC that is comparing an investigational agent against an approved VEGF therapy.

> All patients in TIVO-1 had clear cell RCC, had undergone a prior nephrectomy, and had not previously been treated with either a VEGF or mTOR therapy. Based on the top-line analysis of events in TIVO-1, determined by a blinded, independent review committee, key top-line findings include:
>
> - tivozanib demonstrated a statistically significant improvement in PFS with a median PFS of 11.9 months compared to a median PFS of 9.1 months for sorafenib in the overall study population
>
> - tivozanib demonstrated a statistically significant improvement in PFS with a median PFS of 12.7 months compared to a median PFS of 9.1 months for sorafenib in the pre-specified subpopulation of patients who were treatment naïve (no prior systemic anti-cancer therapy); this subpopulation was approximately 70% of the total study population
>
> - tivozanib demonstrated a well-tolerated safety profile consistent with the Phase 2 experience; the most commonly reported side effect was hypertension, a well- established on-target and manageable effect of VEGFR inhibitors

61. The statements contained in Paragraph 60 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the TIVO-1 trial was not conducted globally as specified, but was instead conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the TIVO-1 trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) that the design defects described in (a), (b), and (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; and (e) that while tivozanib

demonstrated advantages in certain safety categories, tivozanib was inferior to sorafenib in the most significant safety measure, risk of death as measured by overall survival.

62. Later on January 3, 2012, the Company held an investor conference call in which Defendant Ha-Ngoc reiterated the results described in the press release issued that day, and falsely stated that TIVO-1 "was designed and conducted with utmost rigor."

63. The statements identified in Paragraph 62 above were false and misleading when made because TIVO-1 was not designed and conducted with rigor at all, but instead was riddled with severe design defects, and because the statements omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the TIVO-1 trial was not conducted globally as specified, but was instead conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the TIVO-1 trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) that the design defects described in (a), (b), and (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; and (e) that while tivozanib demonstrated advantages in certain safety categories, tivozanib was inferior to sorafenib in the most significant safety measure, risk of death as measured by overall survival.

64. During the January 3, 2012 investor conference call, Defendant Ha-Ngoc was directly asked about overall survival data by George Farmer, an analyst from Canaccord:

> **<Q- George Farmer>** Hi, thanks. How much overall survival do you have and do you need to get – do you need to have for your NDA submission?
>
> **<A- Tuan Ha-Ngoc>** Bill?
>
> **<Q- William Schlichenmyer>** Yeah, George. Great question. To-date, including at the recent December ODAC, FDA has reaffirmed that PFS is an approvable endpoint in RCC, and a good measure of clinical benefit in this setting, and so we feel that OS will not be necessary. It is a secondary endpoint of the study, the overall survival data are not mature though, so that will take some time. And we just want to reaffirm the design of the trial reflects feedback that we obtained – regarding the choice of the primary endpoint – reflects feedback that we obtained in the meetings early on with the both FDA and EMA.

65. The statements identified in Paragraph 64 above were materially false and misleading when made because the TIVO-1 trial was not conducted in the manner discussed with the FDA, and because the FDA had in fact expressly requested overall survival as part of the TIVO-1 trial in the early meetings. Moreover, the statements omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that Defendants had implemented an off-protocol crossover design that was not discussed with the FDA and that confounded study results; (b) that Defendants had elected to conduct TIVO-1 contrary to the global specification discussed with the FDA, instead basing the trial almost exclusively in Eastern and Central Europe, geographies where the treatment of renal cell carcinoma was not comparable to the United States, further confounding study results; and (c) that although the data were not yet fully mature, Defendants had over a year of overall survival data that demonstrated an unmistakeable and worsening trend whereby

patients randomized to tivozanib were dying at higher rates than patients randomized to sorafenib.

66. On February 14, 2012, the Company issued a press release announcing its 2011 financial results, and reviewed key progress achieved with its tivozanib development programs in the fourth quarter of 2011. The Company stated the following, in relevant part:

> "The recent success of our Phase 3 registration trial of tivozanib in RCC, TIVO-1, marks an important milestone for AVEO as we prepare for our first NDA submission later this year," said Tuan Ha-Ngoc, president and chief executive officer of AVEO. "Tivozanib's favorable efficacy and tolerability have now been demonstrated in two large, well-controlled studies. We believe the longest median progression-free survival reported to-date in a first-line pivotal trial in treatment naïve RCC patients combined with its well-tolerated safety profile positions tivozanib to provide patients with a significantly differentiated treatment option."
>
> Fourth Quarter 2011 Key Accomplishments:
>
> Completed top-line analysis of pivotal tivozanib Phase 3 trial, TIVO-1: Notably, in the fourth quarter, AVEO completed top-line analysis of TIVO-1, a global, randomized, Phase 3, superiority clinical trial evaluating the efficacy and safety of tivozanib compared to sorafenib in 517 patients with advanced renal cell carcinoma (RCC). Top-line data were announced in January 2012 and showed that tivozanib successfully demonstrated superiority over sorafenib in the primary endpoint of progression-free survival (PFS) in TIVO-1. Key top-line findings from TIVO-1 include:
>
> Tivozanib demonstrated a statistically significant improvement in PFS with a median PFS of 11.9 months compared to a median PFS of 9.1 months for sorafenib in the overall study population.

67. The statements identified in Paragraph 66 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the TIVO-1 trial was not conducted globally as specified, but was instead conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented,

ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the TIVO-1 trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) that the design defects described in (a), (b), and (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; and (e) that while tivozanib demonstrated advantages in certain safety categories, tivozanib was inferior to sorafenib in the most significant safety measure, risk of death as measured by overall survival.

68. On February 28, 2012, Defendant Johnston made a presentation to investors at the RBC Capital Markets Global Healthcare Conference. In that conference, Defendant Johnston stated that "the data are clear" for tivozanib, and that tivozanib had "the best PFS [progression-free survival] and the safety profile is clearly superior."

69. The statements identified in Paragraph 68 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the TIVO-1 trial was not conducted globally as specified, but was instead conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the TIVO-1 trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the

tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) that the design defects described in (a), (b), and (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; and (e) that while tivozanib demonstrated advantages in certain safety categories, tivozanib was inferior to sorafenib in the most significant safety measure, risk of death as measured by overall survival.

70. On March 30, 2012, the Company filed with the SEC on Form 10-K its annual report for the period ending December 31, 2011. The annual report, which was signed by Defendants Ha-Ngoc and Johnston, stated in relevant part:

> Tivozanib, our lead product candidate, which we partnered with Astellas Pharma Inc., or Astellas, in 2011, is a potent, selective, long half-life inhibitor of all three vascular endothelial growth factor, or VEGF, receptors that is designed to optimize VEGF blockade while minimizing off-target toxicities. Our clinical trials of tivozanib to date have demonstrated a favorable safety and efficacy profile for tivozanib. In January 2012, we announced top-line data from our global, phase 3 clinical trial comparing the efficacy and safety of tivozanib with Nexavar® (sorafenib), an approved therapy, for first-line treatment in renal cell carcinoma, or RCC, which we refer to as the TIVO-1 study. The TIVO-1 study is being conducted in patients with advanced clear cell RCC who have undergone a prior nephrectomy (kidney removal) and who have not received any prior VEGF- and mTOR-targeted therapy. In this trial, we measured, among other things, each patient's progression-free survival, or PFS, which refers to the period of time that began when a patient entered the clinical trial and ended when either the patient died or the patient's cancer had grown by a specified percentage or spread to a new location in the body. PFS is the primary endpoint in the TIVO-1 study. In the TIVO-1 study, tivozanib demonstrated a statistically significant improvement in PFS over Nexavar with a median PFS of 11.9 months for tivozanib compared to a median PFS of 9.1 months for Nexavar in the overall study population. Tivozanib also demonstrated a statistically significant improvement in PFS with a median PFS of 12.7 months compared to a median PFS of 9.1 months for Nexavar in the pre-specified subpopulation of patients who received no prior systemic anti-cancer therapy for metastatic disease—a subpopulation that comprised approximately 70% of the total study population. In the TIVO-1 study, tivozanib demonstrated a well-tolerated safety profile consistent with the results from our tivozanib phase 2 clinical trial in patients with advanced RCC; the most commonly reported side effect was hypertension, a well-established on-target and manageable effect of VEGF receptor inhibitors. The most common treatment-related side effects seen in the phase 2 clinical trial were hypertension (44.9%) and dysphonia, or hoarseness of voice (21.7%). Additionally, the incidence of

> other side effects in the phase 2 clinical trial that are commonly associated with other VEGF receptor inhibitors, such as diarrhea, rash, mucositis, stomatitis, fatigue, and hand-foot syndrome, was relatively low.

71. The statements identified in Paragraph 70 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the TIVO-1 trial was not conducted globally as specified, but was instead conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the TIVO-1 trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) that the design defects described in (a), (b), and (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; and (e) that while tivozanib demonstrated advantages in certain safety categories, tivozanib was inferior to sorafenib in the most significant safety measure, risk of death as measured by overall survival.

72. On May 3, 2012, the Company issued a press release announcing financial and operational results for the first quarter of 2012. With respect to the TIVO-1 trial, the press release stated:

> Successful achievement of primary endpoint and positive top-line results reported from TIVO-1: In January 2012, AVEO announced top-line data from TIVO-1 (Tivozanib Versus Sorafenib in 1st line RCC), a global, randomized, Phase 3, superiority clinical trial evaluating the efficacy and safety of tivozanib compared to sorafenib in 517 patients with advanced renal cell carcinoma (RCC), which showed that tivozanib successfully demonstrated superiority over sorafenib in the primary endpoint of progression-free survival (PFS) in TIVO-1. In TIVO-1,

> tivozanib also demonstrated a well-tolerated safety profile generally consistent with the Phase 2 experience in RCC. We believe that the efficacy and safety profile consistently demonstrated by tivozanib and recently validated in our Phase 3 TIVO-1 trial represent an important step forward in the treatment of patients who have advanced RCC.

73. The statements identified in Paragraph 72 above were materially misleading when made because the safety and efficacy of tivozanib were not "validated" in TIVO-1, and because the statements omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the TIVO-1 trial was not conducted globally as specified, but was instead conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the TIVO-1 trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) that the design defects described in (a), (b), and (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; and (e) that while tivozanib demonstrated advantages in certain safety categories, tivozanib was inferior to sorafenib in the most significant safety measure, risk of death as measured by overall survival.

74. On May 9, 2012, the Company filed with the SEC on Form 10-Q its quarterly report for the period ending March 31, 2012. The filing, which was signed by Defendant Johnston, discussed the TIVO-1 clinical trial and stated that: "[o]ur clinical trials of tivozanib to date have demonstrated a favorable safety and efficacy profile for tivozanib."

75. The statements identified in Paragraph 74 above were materially misleading when made because the trials of tivozanib did not demonstrate a favorable safety profile, and because the statements omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the TIVO-1 trial was not conducted globally as specified, but was instead conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the TIVO-1 trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) that the design defects described in (a), (b), and (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; and (e) that while tivozanib demonstrated advantages in certain safety categories, tivozanib was inferior to sorafenib in the most significant safety measure, risk of death as measured by overall survival.

76. On May 16, 2012, the Company issued a press release announcing positive findings from TIVO-1 entitled, "Superiority Study of Tivozanib in First-Line Advanced RCC." The press release stated in relevant part:

> TIVO-1 is the first superiority pivotal study in first-line advanced renal cell carcinoma (RCC) in which an investigational agent (tivozanib) has demonstrated statistically significant and clinically meaningful progression-free survival (PFS) superiority versus an approved targeted agent (sorafenib) in advanced RCC.
>
> "TIVO-1 is novel in that this Phase 3 clinical study used an approved targeted comparator drug to evaluate first-line RCC treatment," said Dr. Motzer. "Patients

> in the study who had no prior treatment for advanced kidney cancer and who were given tivozanib met the primary PFS endpoint and tolerated the drug well."
>
> A total of 517 patients were randomized to tivozanib (N=260) or sorafenib (N=257). The performance status and other prognostic indicators of patients enrolled in this study were consistent with other pivotal trials in first-line advanced RCC.
>
> "Despite recent advances in the treatment of kidney cancer, patients are in need of new options which are effective and well-tolerated," said Daniel George, M.D., director, GU Medical Oncology and director, prostate clinic, Duke University. "The superior PFS and favorable tolerability demonstrated by tivozanib in TIVO-1 represents an important potential step forward for patients in the treatment of kidney cancer."

77. The statements identified in Paragraph 76 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the TIVO-1 trial was not conducted globally as specified, but was instead conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the TIVO-1 trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) that the design defects described in (a), (b), and (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; and (e) that while tivozanib demonstrated advantages in certain safety categories, tivozanib was inferior to sorafenib in the most significant safety measure, risk of death as measured by overall survival.

78. The May 16, 2012 press release also announced preliminary information regarding overall survival indicating a one-year overall survival rate of 81% for the sorafenib arm versus 77% for the tivozanib arm, but strongly encouraged investors to ignore these results by: (a) characterizing them as "preliminary," "interim" and "not mature;" (b) claiming that the disparity was caused by subsequent therapy in the sorafenib arm, when that was merely a hypothesis rather than a proven fact; (c) omitting that the FDA had expressly requested them to analyze overall survival between the two arms; and (d) omitting that their own scientific misconduct in study design rendered the data uninterpretable.

79. On or about this date, the Company and certain executives and advisors conducted a pre-NDA meeting with the FDA regarding the NDA for tivozanib. A pre-NDA meeting is the most important meeting in the drug development process. The Company has not indicated which AVEO officers and advisors participated in the pre-NDA meeting. However, it is expected that, at a minimum, Defendants Ha-Ngoc and Slichenmyer participated in the meeting because the participation of the Chief Executive Officer and Chief Medical Officer in crucial meetings with the FDA would be standard practice for a company of AVEO's size, especially when it involved the company's flagship drug candidate.

80. In the pre-NDA meeting, the FDA expressed concern that the Company's sole pivotal clinical trial demonstrated an adverse trend in overall survival. The Company continues to refuse to disclose the full minutes from this meeting to investors, but in a post-Class Period conference call dated June 11, 2013, Defendant Slichenmyer admitted that the FDA's official minutes from the May 2012 pre-NDA meeting stated:

> The agency expressed a concern about the adverse trend in overall survival. Further discussion of these findings will be required at the time of filing, and if the application is filed, there will be a review issue that could affect approvability. The FDA recommended that the

> sponsor conduct a second adequately-powered randomized trial in a population comparable to that in the U.S.

Slichenmyer also admitted in June 2013 that the agency requested that Defendants postpone the NDA submission in order to include the results from the final overall survival analysis that Slichenmyer had previously told investors would not be necessary. *See* ¶ 138.

81. Days later, on May 20, 2012, Defendant DePinho appeared on CNBC, where he was interviewed by financial journalist Maria Bartiromo. Although he was booked to discuss drug stocks generally based on his experience as President of University of Texas's MD Anderson Cancer Center, DePinho used the opportunity to hype the prospects for AVEO shares, promising investors that AVEO had a "very effective drug that has a superior safety profile for renal cell cancer, a major unmet need." DePinho would have known at the time of these statements, at a minimum, that the safety profile of the TIVO-1 trial demonstrated a higher risk of death (overall survival) for tivozanib patients because: (1) as a director he was briefed quarterly by senior executives at board meetings and otherwise kept informed of key developments facing the Company; and (2) DePinho's wife, with whom he was in regular communication, was also briefed on developments even more frequently as a member of AVEO's scientific advisory board.

82. DePinho's statements identified in Paragraph 81 above were materially false and misleading when made because tivozanib fell short of its peers by the most important safety measure – the ability to keep patients alive and because renal cell cancer was not an "unmet need," as that term is used in the pharmaceutical context. In addition, DePinho's statements omitted the following material adverse information necessary to make his claims regarding the safety and efficacy of tivozanib not misleading under the circumstances in which they were made: (a) that the tivazonib trial was conducted almost entirely in sites in Central and Eastern

Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) the design defects described in (a), (b), and (c) were so severe that they rendered the results of the tivazonib trial uninterpretable; and (e) the FDA had expressed concerns about the adverse overall survival results and for that reason requested a second trial in a population comparable to the United States.

83. On June 4, 2012, Defendants AVEO, Ha-Ngoc and Slichenmyer made a presentation to investors related to the data presented by the Company at the annual American Society of Clinical Oncology ("ASCO") meeting. In the presentation, Defendant Slichenmyer regurgitated the Company line that overall survival information was "not sufficiently mature" to discuss and instead discussed safety without mentioning that more tivozanib-randomized patients were dying than those in the control arms.

84. The statements identified in Paragraph 83 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) the Company had already received substantial overall survival data, and while not fully mature it evidenced an unmistakeable and worsening trend in overall survival for those patients randomized to the tivazonib arm; (b) the FDA had expressed concern to the Company regarding the adverse trend

in overall survival; (c) the FDA's concerns were sufficiently significant to raise questions on the agency's part as to whether the Company should even seek approval for the drug; (d) the FDA had already requested that the Company delay filing its NDA until it was able to include a full analysis of overall survival data; (e) that the Company's ability to ascertain the cause of adverse overall survival data was confounded by the design defects it chose to introduce into the TIVO-1 study, contrary to study protocol and without discussing with the FDA; and (f) because of the agency's concerns regarding overall survival, the FDA requested that the Company conduct an additional well-designed trial in a population comparable to the United States.

85. On June 5, 2012, Defendants AVEO and Johnston made a presentation to investors at the Jeffries & Co. Health Care conference, where Defendant Johnston stated with respect to tivozanib and the TIVO-1 clinical trial:

> So in oncology, efficacy is the ticket to the dance, and we think we have demonstrated that with the longest PFS show to-date. But TIVO also showed superior safety when compared to sorafenib in this trial, and sorafenib is considered one of the safest TKIs [tyrosine-kinase inhibitors] that's available.

86. The statements described in Paragraph 85 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that contrary to trial protocol, the TIVO-1 trial was conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib

(experimental) arm following an adverse reaction, compromising progression-free survival results; (d) that the design defects described in (a), (b), and (c) were so severe that they rendered the results of the tivazonib trial uninterpretable; (e) that the FDA had expressed concern to the Company regarding the adverse trend in overall survival; (f) that the FDA's concerns were sufficiently significant to raise questions on the agency's part as to whether the Company should even seek approval for the drug; (d) the FDA had already requested that the Company delay filing its NDA until it was able to include a full analysis of overall survival data; (g) that the Company's ability to ascertain the cause of adverse overall survival data was confounded by the design defects it chose to introduce into the TIVO-1 study, contrary to study protocol and without discussing with the FDA; and (h) that because of the agency's concerns regarding overall survival, the FDA requested that the Company conduct an additional well-designed trial in a population comparable to the United States.

87. On August 2, 2012, AVEO issued a press release announcing its second quarter 2012 financial and operating results. In this press release, AVEO made a partial disclosure of the regulatory concerns it had received in May 2012. In a paragraph entitled "Regulatory Update," AVEO stated:

> The FDA has expressed concern regarding the OS trend in the TIVO-1 trial and has said that it will review these findings at the time of the NDA filing as well as during the review of the NDA. AVEO is conducting additional analyses to be included in the NDA submission that demonstrate that the OS data from TIVO-1 are consistent with improved clinical outcomes in RCC patients receiving more than one line of therapy; analyses that the company believes will directly address this issue. AVEO is continuing to work toward submitting the NDA by the end of the third quarter; however, there is a chance that the additional OS analyses may cause the submission to move into the fourth quarter.

88. In reaction to the August 2, 2012 partial disclosure, AVEO shares dropped approximately 27% on very high volume, from $13.30 to close at $9.75. The drop, however, would have been much worse had AVEO disclosed the full truth. AVEO was able to limit the decline in its stock price by continuing to conceal the most damaging regulatory communications conveyed during the May 2012 pre-NDA meeting. Namely, Defendants continued to omit that the FDA had recommended a second adequately-powered trial in a comparable population, that the agency questioned whether the NDA should be filed at all, and that the FDA had expressly warned that adverse overall survival trends could affect approvability. Moreover, the Company's representations regarding an *ad hoc* analysis of overall survival data were further misleading because they omitted the material adverse information that the FDA had never even remotely suggested to AVEO that negative overall survival could be explained by an *ad hoc* explanation of completed trial data; to the contrary, the FDA has always required that safety as well as efficacy be established by credible evidence, not supposition.

89. On August 7, 2012, the Company filed with the SEC on Form 10-Q a quarterly report for the period ending, June 30, 2012. The quarterly report, which was signed by Defendant Johnston, stated in relevant part:

> Tivozanib, our lead product candidate, the development of which is part of our 2011 partnership with Astellas Pharma Inc., or Astellas, is a potent, selective, long half-life inhibitor of all three vascular endothelial growth factor, or VEGF, receptors that is designed to optimize VEGF blockade while minimizing off-target toxicities. Our clinical trials of tivozanib to date have demonstrated a favorable safety and efficacy profile for tivozanib. In May 2012, we announced detailed data from our global, phase 3 clinical trial comparing the efficacy and safety of tivozanib with Nexavar® (sorafenib), an approved therapy, for first-line treatment in advanced renal cell carcinoma, or RCC, which we refer to as the TIVO-1 study. The TIVO-1 study is being conducted in patients with advanced clear cell RCC who have undergone a prior nephrectomy (kidney removal) and who have not received any prior VEGF- and mTOR-targeted therapy. In this trial, we measured, among other things, each patient's progression-free survival, or PFS, which refers to the period of time that began when a patient entered the clinical trial and ended

> when either the patient died or the patient's cancer had grown by a specified percentage or spread to a new location in the body. PFS is the primary endpoint in the TIVO-1 study.

90. The statements identified in Paragraph 89 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that contrary to trial protocol, the TIVO-1 trial was conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the TIVO-1 trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) the design defects described in (a), (b), and (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; (e) that due to concerns regarding overall survival the FDA had even questioned whether the Company should even seek approval for the drug; (f) the FDA had requested that the Company delay filing its NDA until it was able to include a full analysis of overall survival data; (g) that the Company's ability to ascertain the cause of adverse overall survival data was confounded by the design defects it chose to introduce into the TIVO-1 study, contrary to study protocol and without discussing with the FDA; and, most importantly, (h) because of the agency's concerns regarding overall survival, the FDA requested that the Company conduct an additional well-designed trial in a population comparable to the United States.

91. On August 16, 2012, Defendants AVEO and Johnston made a presentation to investors at the Canaccord Genuity Global Growth Conference, stating in relevant part:

> In sorafenib's pivotal trial, they had a 65% overall survival after the first year. Pazopanib showed 73% overall survival at the one-year timeframe, and Sutent, or sunitinib, showed 78%. In our trial, the tivozanib arm was 77% overall survival. And interestingly, the sorafenib arm showed 81% overall survival. When we met with the FDA in our pre-NDA meeting, this caught their eye, and it's – properly, it's the FDA's job to present safe and effective drugs to the U.S. population. And even though overall survival in this therapy is not an approvable endpoint, this is – the overall survival trend is moving in a different direction than PFS, and they expressed some concern and they would like an explanation. So along those lines, we are doing a lot of analyses to help to address their concern, and we expect to do so as we file our NDA later this quarter.

92. The statements identified in Paragraph 91 above were materially false and misleading when made because overall survival is an approvable endpoint for cancer drugs (though one that AVEO wanted to portray as unimportant because tivozanib's overall survival data was unfavorable), and because the statements omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that when AVEO met with the FDA in the pre-NDA meeting, the FDA requested far more than an explanation – it requested that AVEO conduct an additional well-designed Phase III clinical trial in a population comparable to the United States; and (b) due to concerns regarding overall survival, the FDA questioned whether an NDA should be filed at all.

93. On September 10, 2012, Defendants AVEO and Johnston made a presentation to investors at the Morgan Stanley Global Healthcare Conference, wherein Defendants were expressly asked about overall survival data and regulatory communications with the FDA, and gave materially misleading answers:

Marshall Urist (moderator)

Okay, great. Well, with that why don't we start, of course, with TIVO and maybe we can chat about some of the – some of your recent discussions with the FDA about the overall survival analyses. So maybe just give a quick overview of the issue for people. And then where are your discussions currently and updated thoughts on this process.

David B. Johnston

Certainly. So, this goes back to the design of our Phase III trial, which was a head-to-head or it's the first trial done in the RCC space pivotal trial that used an active targeted comparator, in this case, sorafenib, most of the trials have either used interferon or something like that or even a placebo. So it's tivozanib versus sorafenib. The design of the trial was a one-way crossover. Upon progression if you were initially randomized to the sorafenib arm, you were then eligible and then you progressed, you had confirmed progression. You were then eligible to receive tivozanib following that.

If you were originally randomized on the TIVO arm and you progressed, there was no prescribed crossover, it was the physician's choice or, depending on the geography, best supportive care. And that combined with the geographies where the majority of these sites were, which is mainly Eastern Europe, Ukraine, Russia, Poland et cetera, in many cases, there was no second line therapy or effective second line therapy available for the TIVO arm, whereas on the sorafenib arm, they almost all received TIVO.

So the result of that was when we first went to the FDA in the spring, we just presented top line data for our pre-NDA meeting. What they saw was in the one-year survival percentages of the two arms, those who were randomized to the sorafenib arm, once again those who are eligible to receive TIVO for second line had an 81% survival rate after one year. And those patients who have been originally randomized to the tivozanib arm had a 77% survival rate.

Now that led the FDA to then say, this is something that we need you to explain, and we expect to see it in your NDA submission and we expect to see from overall survival et cetera. So that's what we're up with the FDA on now.

94. The statements identified in Paragraph 93 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA

requested far more than an explanation of adverse overall survival data – it requested that AVEO conduct an additional well-designed Phase III clinical trial in a population comparable to the United States; (b) that the FDA had expressly warned Defendants that the adverse trend could affect approvability, and questioned whether an NDA should even be filed; (c) that the design defects Defendants discussed in these statements regarding the TIVO-1 trial, the one-way crossover and the overwhelming focus on Central European and Eastern European patients, were contrary to pre-specified trial protocol and not discussed with the FDA prior to trial initiation; and (d) the FDA had never even remotely suggested that the adverse overall survival data and fatal trial design defects could be overcome by additional *post hoc* analyses massaging data from the TIVO-1 trial.

95. On September 20, 2012, Defendants AVEO and Johnston made a presentation to investors at the UBS Global Healthcare Conference, stating in relevant part:

> **David B. Johnston:**
>
> One of the features of this Phase III trial was a unique one-way crossover design. In the design of this trial, we had input from our principal investigator, Bob Motzer out of Sloan-Kettering, as well as some of the investigators from our Phase II, who strongly suggested that we provide tivozanib to every patient that wants it at some time during the trial.
>
> So we designed a trial that had tivozanib head-to-head versus sorafenib and if you were on the tivozanib arm and you progressed, you were then moved on to the regional standard of care or the physician's choice. The reason that's important is because the region where this trial was primarily done was Eastern Europe. Poland, Ukraine, Russia was the vast majority of the patients. If you were on the sorafenib arm and you progressed, you had the choice and you could be provided tivozanib for second line treatment, or you could choose physician's choice.
>
> If you look at percentage of overall survival after one year that other trials have shown – other pivotal trials, the sorafenib pivotal trial showed 65% of the patients had survived after one year, the pazopanib was 73% and sunitinib or Sutent was 78% in their pivotal

> trial. For the TIVO-I study, 77% of the patients initially randomized to tivozanib had survived after the 12-month – at the 12-month snapshot. The sorafenib arm showed 81% overall survival. And that was a statistic that was noted at our pre-NDA meeting with the FDA. They were rightly concerned with the fact that the overall survival trends were going in a different direction of PFS. Now at that time, they didn't see any backup analysis.
>
> There was no explanation. They simply said, we need to understand this. And we think that's the right thing.

96. The statements identified in Paragraph 95 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA requested far more than an explanation of adverse overall survival data – it requested that AVEO conduct an additional well-designed Phase III clinical trial in a population comparable to the United States; (b) that the FDA had expressly warned Defendants that the adverse trend could affect approvability, and questioned whether an NDA should even be filed; and (c) that the design defects Defendants discussed in these statements regarding the TIVO-1 trial, the one-way crossover and the overwhelming focus on Central European and Eastern European patients, were contrary to pre-specified trial protocol and not discussed with the FDA prior to trial initiation.

97. On September 28, 2012, the Company issued a press release announcing that AVEO had submitted an NDA to the FDA seeking approval for tivozanib in patients with advanced rencal cell carcinoma. The press release stated in relevant part:

> The NDA submission is based on results of the global Phase 3 TIVO-1 (Tivozanib Versus Sorafenib in 1st line Advanced RCC) trial, a randomized superiority-designed pivotal trial evaluating the efficacy and safety of tivozanib compared to sorafenib in 517 patients with advanced RCC who had no prior treatment with a systemic therapy, as well as data from 17 clinical studies involving over 1,000 subjects who received tivozanib. In TIVO-1, tivozanib demonstrated a statistically significant improvement in progression-free survival (PFS) versus sorafenib, an approved targeted agent, and a favorable tolerability profile.

98. The statements identified in Paragraph 97 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that contrary to trial protocol, the TIVO-1 trial was conducted almost entirely in sites in Central and Eastern Europe, geographies that were not comparable with the United States in the treatment for renal cell cancer; (b) that an off-protocol one-way crossover not specified in the TIVO-1 protocol and not discussed with the FDA was implemented, ensuring that participants in the sorafenib (control) arm would receive a different level of post-treatment therapy than participants in the tivozanib (experimental) arm and confounding overall survival results; (c) that dose reductions in the TIVO-1 trial were implemented in different rates such that dosage was weakened far more for patients in the sorafenib (control) arm than the tivozanib (experimental) arm following an adverse reaction, compromising progression-free survival results; (d) the design defects described in (a), (b), and (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; (e) that due to concerns regarding overall survival the FDA had questioned whether the Company should even seek approval for the drug; (f) the FDA had requested that the Company delay filing its NDA until it was able to include a full analysis of overall survival data; (g) that the Company's ability to ascertain the cause of adverse overall survival data was confounded by the design defects it chose to introduce into the TIVO-1 study, contrary to study protocol and without discussing with the FDA; and, most importantly, (h) because of the agency's concerns regarding overall survival, the FDA requested that the Company conduct an additional well-designed trial in a population comparable to the United States

99. On November 11, 2012, Defendants AVEO and Johnston made a presentation to investors at the Lazard Capital Markets Healthcare Conference, stating in relevant part:

Johnston:
So the trial was a bit unusual and that it had a one way crossover. This is as far as we can tell on first-line oncology, the first that we can find. There may be others out there, but we haven't been able to find them. So let me describe it to you. If a patient was randomized to tivozanib for first-line and had confirmed disease progression as measured by independent radiological read, they would then move on for second-line treatment, will be the regional standard of care or physician's choice. I'll come back to why that's important in just a moment. If you originally randomize the sorafenib arm and, once again, had confirmed disease progression measured independently, you were then offered a crossover to tivozanib second-line or physician's choice.

The reason why this is important is because this being a first-line VEGF trial, it was done primarily in Eastern Europe, Ukraine, Poland and Russia, where, as it turns out, VEGF TKIs are used with generally for the first-line and they're usually not reimbursed for second-line. And what happened is this. If you look at the left-hand bar here, this is a – this was a cut of patients as of last spring. What you see here is that, at that time, 81 of the patients of the 260 patients on the tivozanib arm were still on first-line therapy. 115 had progressed and had received no – repeat, no second-line therapy, based primarily upon the geographies where they were. 16 had moved on to a VEGF-TKI, which is more and more seen as the most effective second-line therapy. VEGF followed by VEGF is generally seen as the new standard.

Now, what that did is when we had our post – our pre-NDA, rather – conversation with the FDA, the FDA saw – this is all that they saw. They didn't see any backup. All they saw was these two numbers. They didn't see any of the breakdown in terms of the second-line therapies or anything like that.

What caught their eye was that this was moving in a different direction than the relative PFSs. So as you recall, in this population, the PFS – so tivozanib, with the intent-to-treat population, was 11.9 months compared to 9.1. Why is this going a different direction? So the conversation we've been having the FDA – and we recently submitted our NDA in late September – September 27. With that, we submitted a package explaining with a white paper, showing, first of all, final overall – median overall survival as prescribed by the protocol, as well as a series of analyses supporting the hypothesis that, in fact, TIVO being given to the sorafenib arm as second-line therapy is having beneficial impact.

100. The statements identified in Paragraph 99 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA requested far more than a white paper hypothesizing potential causes of adverse overall survival

data – it requested that AVEO conduct an additional well-designed Phase III clinical trial in a population comparable to the United States; (b) that the FDA had expressly warned Defendants that the adverse overall survival trend could affect approvability, and questioned whether an NDA should even be filed; and (c) that the design defects Defendants discussed in these statements regarding the TIVO-1 trial, the one-way crossover and the overwhelming focus on Central European and Eastern European patients, were contrary to pre-specified trial protocol and not discussed with the FDA prior to trial initiation.

101. On January 8, 2013, Defendants AVEO and Ha-Ngoc made a presentation to investors at the J.P. Morgan Global Healthcare Conference, stating in relevant part:

> [O]verall survival is an important secondary end point that we and others watch and we have disclosed to you the interim analysis at one year showing that in the case of tivozanib patients – randomized tivozanib, shows a 77% overall survival versus an 81% in the control arm, noted also that the difference between two arms is not statistically significant.
>
> However, it's interesting to note that looking across trials that the 77% of tivozanib is among the highest percentage across all the other agents. And that is one of the key feature of our study design that allow for crossover, particularly on the control arms progressor into tivozanib as a companion study.
>
> And let me describe to you the chart here in the bottom half of this slide. It shows that on the right-hand side, the patients who progress on sorafenib, of those, 150 of them received effective VEGF therapy and thankfully, all of them, 148, received tivozanib because we provide for free for those who would like to go that way. In comparison, in the patients randomized the tivozanib arm, only 16 patients received effective VEGF therapy, a 1:10 ratio.
>
> So, in essence, when you look at that picture, the overall survival results that I have described in the previous slide is probably a result of a fact that on one hand, on the right-hand side, you have a sequential treatment of two active agents, first sorafenib and tivozanib. And on the left-hand side for tivozanib is essentially a single agent

102. The statements identified in Paragraph 101 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA expressly requested far more than a hypothesis about what "probably" caused tivozanib-randomized patients to die more frequently than control-group patients – it requested that AVEO conduct an additional well-designed Phase III clinical trial in a population comparable to the United States to provide interpretable *evidence* regarding overall survival; (b) that the FDA had expressly warned Defendants that the adverse overall survival trend could affect approvability, and questioned whether an NDA should even be filed; and (c) that the design defects in the TIVO-1 trial, including the one-way crossover and the overwhelming focus on Central European and Eastern European patients, ensured a disparity in second-line therapies between the two study arms and were contrary to pre-specified trial protocol.

103. On January 17, 2013, AVEO announced that it had arranged to sell 6.667 million shares of AVEO common stock in a bought underwriting at an inflated offering price of $7.50 per share, raising approximately $46.7 million after underwriting discounts. This capital raise, which was critical to the Company's future, was facilitated by the inflation of AVEO's share price via the misrepresentations described herein.

104. On February 13, 2013, following the release of fourth quarter 2012 financial results, Defendants AVEO, Ha-Ngoc, Johnston, and Slichenmyer held a conference call for investors. During that call, Defendants AVEO and Slichenmyer stated as follows:

> Turning now to the overall survival data. What's shown here are the protocol specified final OS results, which are being presented publicly for the first time today. The language in the protocol specified that the final OS analysis was to be conducted at the time that all patients in the study have been followed up for at least two years following

> randomization. That time corresponded to the date of August 27, 2012 and we've broaden the data to that point.
>
> This analysis was included in the NDA, which was submitted in September. We expect these results to be a subject of discussion at a future ODAC meeting for which we are preparing. The median overall survival in the tivozanib arm is 28.8 months compared with 29.3 months for the control arm. The hazard ratio is 1.25 and there is a non-significant P value of 0.105.

105. The statements identified in Paragraph 104 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA had expressly requested that AVEO conduct an additional well-designed Phase III clinical trial in a population comparable to the United States to provide interpretable evidence regarding overall survival; (b) that the FDA had not only stated that overall survival would be a review issue, but had expressly warned Defendants that the adverse overall survival trend could affect approvability, and prior to filing questioned whether an NDA should even be filed; and (c) that while the overall survival was measured as specified in the TIVO-1 protocol, the interpretation of overall survival was fatally confounded because of design defects in the TIVO-1 trial, including the one-way crossover and the overwhelming focus on Central European and Eastern European patients, that ensured a disparity in second-line therapies between the two study arms and were contrary to pre-specified trial protocol.

106. In the question-and-answer portion of the February 13, 2013 conference call, Defendants AVEO and Slichenmyer further dissembled regarding regulatory communications with the FDA focusing on overall survival:

> **<Q - Geoff C. Meacham>:** … on OS, when you guys designed TIVO-1, maybe walk us through the conversation with FDA. Was there any contemplation of overall survival? And then, when you have the Eastern European geographic sort of bias and you know that limited availability of other meds is there, was this something that you

> guys could have anticipated when you looked at the design of this, either on its own or when you look at other renal cell agents in these same geographies? Thanks.
>
> **<A - William J. Slichenmyer>:** Geoff, Bill here. And at that time, as the study was being designed, there had been precedents with other phase III trials conducted in the same parts of the world that included one-way crossovers. And in general, overall survival benefit has not been proven, and the reason that the FDA and other health authorities use PFS as an endpoint for registration in RCC is because of the recognized impact of confounding with second and subsequent lines of therapy.
>
> ---
>
> **<Q - Salveen K. Richter>:** Thanks for taking my question. Can you remind us exactly what the FDA was looking for in the additional analysis they requested to understand the overall survival curves?
>
> **<A - William J. Slichenmyer>:** So I think the key thing to note is that we remain confident in the data that we've submitted in the NDA and that we are working with the FDA to address lots of questions they're sending to us, it's difficult at this stage in review process for them to ask for a lot of additional analysis. Overall, we are feeling very optimistic that things are going to continue to do well. And I should just maybe add that as a general point of company policy, we don't disclose details of our discussions with the health authorities.

107. The statements identified in Paragraph 106 above were materially misleading when made because they omitted material adverse information necessary to make the statements not misleading under the circumstances in which they were made. Specifically, they described relatively innocuous parts of the Company's regulatory communications with the FDA but concealed the most damaging parts, including the facts that: (a) the FDA had expressly requested that AVEO conduct an additional well-designed Phase III clinical trial in a population comparable to the United States to provide interpretable evidence regarding overall survival, not just a *post hoc* analysis to come up with a hypothesis that might explain causation; and (b) the one-way crossover and bias to Central and Eastern European sites that confounded overall

survival results were never provided for in the TIVO-1 trial protocol or discussed prior to trial initiation with the FDA.

108. On February 27, 2013, Defendants AVEO and Johnston made a presentation to investors at the RBC Capital Markets Global Healthcare Conference, where they responded falsely to a crucial question from an analyst as follows:

> **Adnan S. Butt**
>
> So the company has been pretty upfront about disclosures, disclosing the OS risk et cetera, OS trend as a concern for the FDA.
>
> **David B. Johnston**
>
> Absolutely.

109. The statements identified in Paragraph 108 above were materially false and misleading when made because neither the Company nor Defendant Johnston had been "upfront" about overall survival risk or their regulatory communications with the FDA regarding overall survival risk. Specifically, Defendants had concealed from investors and analysts: (a) that the FDA had expressly requested that AVEO conduct an additional well-designed Phase III clinical trial in a population comparable to the United States to provide interpretable evidence regarding overall survival; (b) that the FDA had warned AVEO that overall survival could affect approvability; and (c) that the FDA questioned whether the Company should even file an NDA in light of these concerns.

110. On March 11, 2013, the Company filed with the SEC on Form 10-K its annual report for the period ending December 31, 2012. The annual report, which was signed by Defendants Ha-Ngoc and Johnston, stated in relevant part:

> In the TIVO-1 study, tivozanib demonstrated a statistically significant improvement in PFS over Nexavar with a median PFS of 11.9 months for tivozanib compared to a median PFS of 9.1 months for Nexavar in the overall study population. Tivozanib also demonstrated a statistically significant

> improvement in PFS with a median PFS of 12.7 months compared to a median PFS of 9.1 months for Nexavar in the pre-specified subpopulation of patients who received no prior systemic anti-cancer therapy for metastatic disease—a subpopulation that comprised approximately 70% of the total study population.
>
> Overall survival was a secondary endpoint of the TIVO-1 study. The final overall survival, or OS, analysis, as specified by the TIVO-1 protocol, showed a median OS of 28.8 months (95% confidence interval, or CI: 22.5–NA) for the tivozanib arm versus a median OS of 29.3 months (95% CI: 29.3–NA) for the Nexavar arm.

111. The statements identified in Paragraph 110 above were materially misleading when made because they omitted the following material adverse information necessary to make them not misleading under the circumstances in which they were made: (a) that off-protocol design defects in the TIVO-1 trial ensured that the results of TIVO-1 would lack scientific rigor and be uninterpretable; (b) that the FDA had recommended a second adequately-powered trial in a comparable population to provide scientifically-valid evidence regarding overall survival; (c) that the agency questioned whether the NDA should be filed at all; (d) that the FDA had expressly warned that adverse overall survival trends could affect approvability; and (e) that even the progression-free survival results were tainted by the employment of materially different dose reductions ensuring that the effective dose of the control drug, sorafenib, was reduced far more in a dose reduction event than the experimental drug, tivozanib.

112. On March 13, 2013, Defendants AVEO and Johnston made a presentation to investors at the Barclays Capital Global Healthcare Conference, stating in relevant part:

> And lastly and most importantly for us, we need a favorable risk benefit profile. So, if you're here, you probably know that PFS is the accepted registration endpoint for advanced RCC. That's what all the other drugs have been approved on. OS is a secondary endpoint and is often [ph] confounded (5:17). In fact, it's – no drug has shown statistical improvement in overall survival even versus a placebo. The only exception would be the mTOR inhibitor TORISEL in poor prognosis patients, but none of the VEGF TKIs had.
>
> In ours, we had a median OS compared to Sorafenib that had a 28.8 months median compared to 29.3 months on the Sorafenib arm, but it

> has a ratio of about 1.25 favoring the Sorafenib arm. So, what's going on? If you can see here on the bottom, too – there's a pointer here somewhere, but along the bottom you can see the percentage of patients on the control arm who would cross over to Tivozanib. The reason why this is important is because the design of the trial was such that there was a one way crossover so if you are on Sorafenib arm and you progressed, you got Tivozanib. If you are on the Tivozanib arm and you progress, you just got stay into the care and the geography where the trial is being conducted. So, you can see that towards the end of the trial, over 2/3 of the patients had transferred over to Tivozanib.

113. The statements identified in Paragraph 112 above were materially misleading when made because they omitted the following material adverse information necessary to make them not misleading under the circumstances in which they were made: (a) that off-protocol design defects in the TIVO-1 trial ensured that the results of TIVO-1 would lack scientific rigor and be uninterpretable; (b) that none of the referenced trials for other approved drugs demonstrated the same safety risk regarding overall survival as tivozanib; (c) that the FDA had recommended a second adequately-powered trial in a comparable population to provide scientifically-valid evidence regarding overall survival; (d) that the agency questioned whether the NDA should be filed at all; (e) that the FDA had expressly warned that adverse overall survival trends could affect approvability; and (f) that even the progression-free survival results were tainted by the employment of materially different dose reductions ensuring that the effective dose of the control drug, sorafenib, was reduced far more in a dose reduction event than the experimental drug, tivozanib.

THE TRUTH IS REVEALED

114. On April 30, 2013, the FDA released its ODAC Briefing Document, which disclosed for the first time that the FDA had expressly recommended that the Company conduct an additional clinical trial and highlighted the regulatory history of Tivopath previously concealed by the Company, including the fact that the Company disregarded FDA

recommendations for an additional clinical study, "[a] pre-NDA meeting was held in May 2012. Here, the FDA expressed concern about the adverse trend in overall survival in the single Phase 3 trial and recommended that the sponsor [AVEO] conduct a second adequately powered randomized trial in a population comparable to that in the US."

115. The Briefing Document also disclosed that the design of the TIVO-1 trial deviated significantly from that specified in trial protocol and discussed with the FDA in meetings in December 2008 and May 2009. Specifically, the TIVO-1 trial protocol did not include the one-way crossover that Defendants claim confounded overall survival results, and Defendants had not discussed introducing that design defect with the FDA in TIVO-1 design meetings. Moreover, the TIVO-1 trial protocol called for global enrollment rather than biasing study sites to Central and Eastern Europe:

> The Phase 3 study was carried out at 76 sites. It was initiated in February 2010 and was ongoing at the time of submission. As shown in Table 5, *most of the study sites were in Eastern Europe with potentially different standard of care and practice patterns compared to the US.* Patients on the sorafenib arm of the Phase 3 study with PD could receive tivozanib on an extension/crossover study. Patients on the tivozanib arm of the Phase 3 study with PD could receive additional medications. *However, the 2nd line use of targeted therapies was not considered the standard of care in many of the countries participating in the trial.*

Table 5: Geographic Distribution of Patient Accrual		
Geographic Region	Tivozanib N = 260	Sorafenib N = 257
Central/Eastern Europe	229 (88%)	228 (89%)
North America/Western Europe	22 (9%)	18 (7%)
Rest of World	9 (4%)	11 (4%)

> The majority of the patients on the sorafenib arm received tivozanib after the development of INV-determined PD while most of the patients on the tivozanib arm did not receive subsequent targeted therapy. *The majority of patients were enrolled from sites in Central and Eastern Europe where 2nd line targeted therapy was not available. This is not consistent with the practice patterns in the US and it is, therefore, unclear whether the patients in this study were representative of those in the US.*

(emphasis added).

116. The Briefing Document also disclosed flaws in the unproven hypothesis Defendants had offered to investors to assuage investor concerns regarding overall survival – that (according to Defendants) the adverse overall survival results for tivozanib were necessarily caused by differing post-study treatments for patients randomized to sorafenib in the TIVO-1 trial, not long-term risks of tivozanib use. As the FDA noted, subsequent therapies had also been introduced in many of the trials for the seven targeted treatments it had already approved for renal cell carcinoma, but the pivotal studies for those drugs all demonstrated overall survival trends in favor of the candidate drug (unlike tivozanib).

> Adverse events of special interest in the tivozanib arm of the Phase 3 trial include: hypertension (45%), hemorrhage (12%), proteinuria (9%), arterial embolic and thrombotic events (3%), hypothyroidism (5%), GI perforation/fistula (1%), and pancreatitis (0.8%). In the Safety Database, 1 patient developed hepatic failure and a 2nd patient developed posterior reversible encephalopathy syndrome. Note that the incidence of elevated TSH (62%) and proteinuria by dipstick (32%) along with grade 3-4 amylase (5%) and lipase (10%), was much higher than the number of reports of the corresponding adverse events. Importantly, 1 patient died due to pancreatitis.

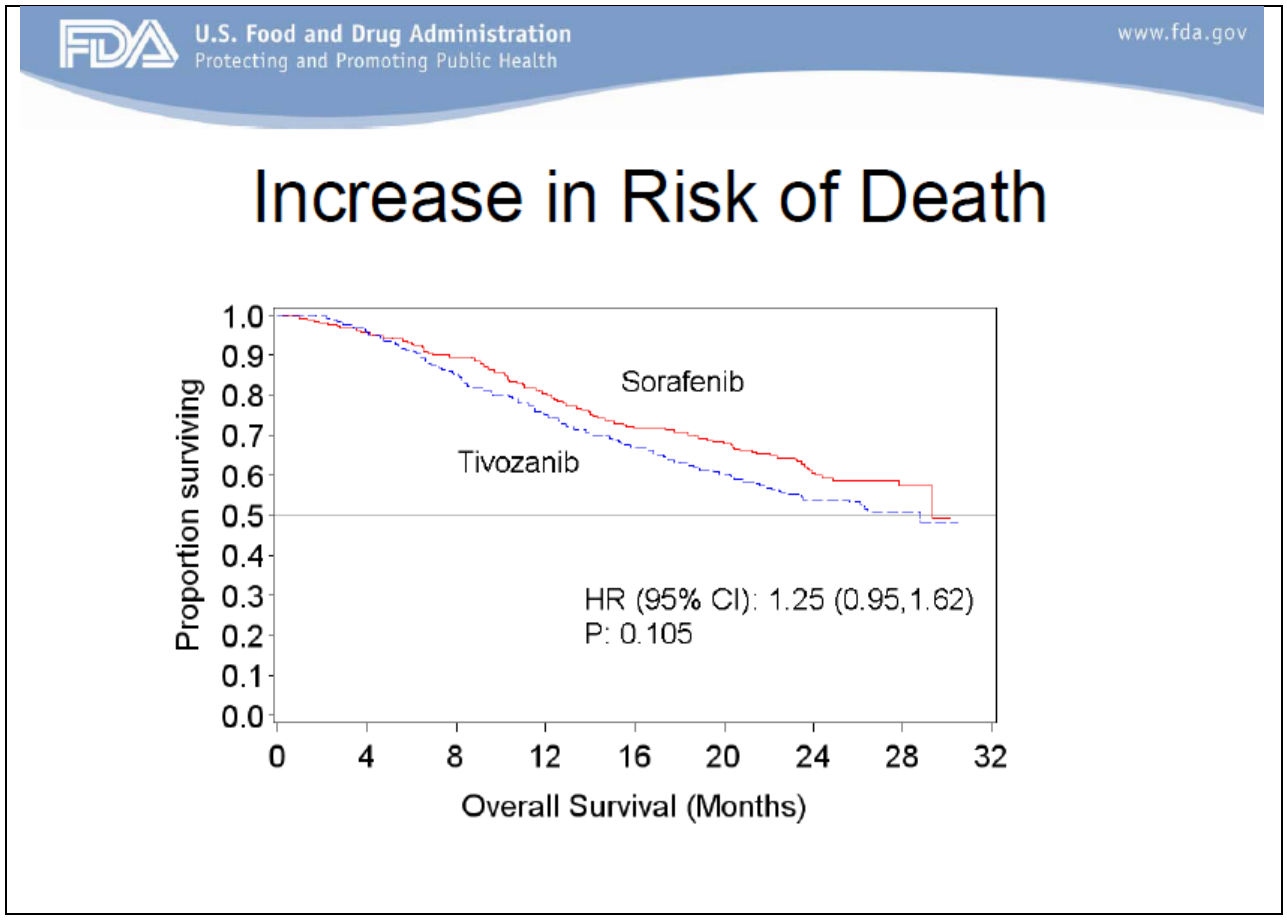
117. In response to the disclosures in the Briefing Document, the Company's shares fell $2.33, or 31.31% per share, to close at $5.11 on April 30, 2013, on volume of over 15 million shares. An article in the Boston Globe confirmed that the decline was due to the new information concealed during the Class Period regarding the FDA's May 2012 request for an additional clinical trial:

> Shares of AVEO Pharmaceuticals Inc. plummeted more than 30 percent Tuesday after the Food and Drug Administration said another

> clinical trial may be needed to weigh the risks and benefits of the Cambridge company's kidney cancer treatment.[3]

118. In the May 2, 2013 hearing before the ODAC panel, the FDA disclosed further information about the regulatory communications and scientific misconduct that the Company had concealed during the Class Period. Indeed, Dr. Ibrahim, Deputy Director of the FDA's Division of Oncology Products 1, explained that the ODAC panel was convened in order to address the agency's concerns regarding higher risk of death (lower overall survival) for tivozanib patients: "Why are we here for this morning's session at ODAC? We are here because we would like to discuss with you a trial that has been submitted, which has shown a concerning increase in the risk of death from the investigational drug tivozanib." According to the FDA, this higher risk of death was indicated by an industry-standard Kaplan-Meier curve which showed "a 25 percent potential increase in the risk of death with tivozanib as compared to sorafenib." The Kaplan-Meier curve, included on the slide reproduced below that the FDA used at the ODAC panel, demonstrated a higher risk of death for tivozanib patients early in the trial, and broadening as time progressed:

[3] R. Weisman, "Shares of AVEO Phamaceuticals plummet as FDA weighs new clinical trial for kidney cancer drug," *Boston Globe*, April 30, 2013.



119. ODAC panel member Dr. Serekes pointed out, and Defendant Slichenmyer was forced to acknowledge in response, that the adverse overall survival trend between tivozanib and sorafenib was evidenced within six months after treatment began. Accordingly, there is no legitimate basis to believe that the adverse trend was not well known to AVEO and its executives at all times during the Class Period, which begins over thirteen months after TIVO-1 trial commenced enrollment.

120. Dr. Jarow, the FDA's lead presenter, explained why the agency wanted to assess overall survival under tivozanib, as the agency made clear to Defendants in December 2008 and May 2009:

> Why do we care so much about overall survival? Progression-free survival is a composite endpoint of disease progression measured by radiological scans and death. An improvement in progression-free survival of a certain magnitude may be a clinical benefit in and of itself for renal cell carcinoma.
>
> In this study, 92 percent of the progression events were radiological. In other words, there were very few deaths during the actual study. PFS and OS endpoints are often aligned. Overall survival captures both the efficacy and toxicity of a drug. However, the two endpoints may not always be aligned, such as when drugs have increased toxicity. Therefore, we depend on overall survival to assess the risk/benefit profile of a drug.

121. Dr. Arrington, who led the FDA's presentation on safety at the ODAC panel, explained that tivozanib demonstrated a higher risk of death no matter how the data was sliced, and that the risk may be attributable to lasting effects of tivozanib's toxicity:

> As was presented previously, this slide shows the Kaplan-Meier curves for overall survival, showing a 25 percent potential increase in the risk of death on the tivozanib arm. This is clearly a concerning efficacy and safety finding in this study.
>
> Here we see that regardless of how one approaches the data on deaths in this phase 3 trial, there were more deaths on the tivozanib arm than there were on the sorafenib arm. For death within 30 days, there were more deaths attributed to progressive disease on the tivozanib arm. But, as we know, attribution may be unreliable, especially in an unblinded trial.
>
> When we looked at the number of adverse events reported by region, we saw that there are marked regional differences in the number of patients reporting a grade 3 to 4 adverse event. There were 88 percent and 75 percent reporting a grade 3 to 4 adverse event in North America, Western Europe, and other countries versus the 59 percent in the Central and Eastern European region.
>
> Again note that the majority of patients were enrolled in Central and Eastern Europe, 456, and that the number of patients recruited in the other two regions is small, 60 patients in total. With this small number of patients, we cannot draw firm conclusions concerning regional differences.
>
> The differences observed could be due to the differences in toxicities, experienced as a result of the characteristics of the patient population, or there may be differences in ascertainment or reporting bias.

> Certainly, this finding does make us question the applicability of the adverse event profile obtained in this study to the U.S. population.

122. Dr. Ibrahim of the FDA emphasized that sponsor companies developing oncologic drugs were consistently warned that overall survival was an important measure for approval even where progression free survival was a primary endpoint:

> FDA has consistently informed sponsors in meetings and public presentations that while FDA will accept PFS as the primary endpoint for certain disease settings, overall survival remains an important efficacy and safety endpoint. PFS may serve as a primary endpoint in trials for practical reasons, but overall survival is generally considered to be of ultimate clinical benefit.

123. In contrast to Defendants' Class Period attempts to portray tivozanib's overall survival data as unremarkable or expected, Dr. Ibrahim made clear that the agency had never before approved a similar treatment that showed inferior overall survival: "Multiple drugs have been approved for metastatic renal cell cancer, but none of them had this concerning issue. In fact, no approved oncology drug has raised this kind of concern for a detriment in survival in recent trials that served as a basis for marketing approval."

124. Critically, Dr. Ibrahim explained that Defendants' attempt to guess at the reason why tivozanib patients experienced a higher risk of death simply was not clinical evidence upon which an approval could be based:

> In the NDA submission and the briefing document, the applicant provides an imbalance in post-study therapy as the reason for inconsistency between PFS and overall survival.
>
> It is possible that tivozanib is an effective drug, and the sequential use after sorafenib improved survival on the sorafenib arm. But there may be other reasons as well, and these include that sorafenib is superior compared to tivozanib in terms of overall survival, and the very real possibility that death from toxicity contributed to a worse survival on the tivozanib arm.
>
> FDA requires adequate and well-controlled studies for approval. This study was not well-controlled for post-study treatments. In addition, consideration should be given to false positive rates when these rationales and other post hoc analyses are assessed. The various post

> hoc analyses were done in non-randomized populations, and drawing any inference from them is problematic.
>
> The inconsistent PFS and OS results and imbalance in post-study treatments made the trial's results uninterpretable and inconclusive when making a risk/benefit assessment necessary for approval of a drug.

125. Dr. Jarow of the FDA confirmed that Defendants' rationale for the higher death rates was "just a hypothesis" not proved by evidence:

> The key issue with this application is the inconsistent findings in this single phase 3 trial. A 20 percent benefit in progression-free survival was observed against an active comparator, sorafenib, but we also observe a potential 25 percent increase in the risk of death.
>
> The applicant presents a hypothesis that this is due to confounding by an imbalance in subsequent treatment. However, this cannot be proven based on post hoc exploratory analyses and remains just a hypothesis.

While Dr. Jarow allowed that Defendants' unproved hypothesis might be a "potential cause" of the higher death rates under tivozanib, he noted the hypothesis was inconsistent with evidence from other trials in approved drugs that had previously been published and were known to those conducting research in the field of renal oncology, including Defendants:

> The applicant hypothesizes that the imbalance in subsequent therapy was the cause for the observed decrement in overall survival. However … five of the seven currently approved targeted agents allowed unilateral crossover for their control arm in their pivotal trials, with a rate ranging from 4 percent to as high as 80 percent.
>
> Where data were available, the relative rate of subsequent targeted therapy, which includes both crossover and subsequent therapy given off protocol, was compared for the two arms of each trial. As you can see, there was a significant imbalance in other trials, yet none of these trials demonstrated a negative trend for overall survival.

126. Dr. Pazdur, Director of the FDA's Hematology and Oncology Products' Office of New Drugs, clarified that defects in TIVO-1 made it impossible to tell whether given patient deaths were caused by drug toxicity, disease or other factors:

> We have a study here, basically, and we talking about attribution of death, which is very, very difficult to say why a patient dies, especially when you're dealing with toxicities such as MIs, arterial thrombosis, potential cardiovascular events. We also have an issue of the study being conducted largely outside of the United States with sites that we are unfamiliar with. And secondly and most importantly, this trial is unblinded.
>
> So to try to make some type of statement that we know why this patient died, whether it's from disease or from a drug toxicity is very, very, very confounded.

Dr. Pazdur indicated that these trial defects made it impossible for the FDA to determine whether tivozanib caused greater harm than benefit:

> If I could summarize our biggest fear here, it could be summarize by a statement, do no harm.
>
> ***
>
> We have a difference, a modest difference, in progression-free survival, but almost an equally negative impact on overall survival -- rather, a negative impact on overall survival and a positive impact on progression-free survival. And obviously, overall survival is a much more important clinical endpoint than progression-free survival.

127. Dr. Jarow also criticized the confounding of data caused by Defendants' "flaws in the design and conduct of the phase 3 trial, 301 [TIVO-1]." Specifically, he stated:

> The trial design is problematic for employing unilateral crossover in the setting of an active comparator and for performing the trial in a region where there is limited access to subsequent therapies. This is a potential cause of the confounding of the survival data, and also limits the applicability of these trial results to the U.S. population.
> Less than 10 percent of the patients were recruited from Western Europe and North America, and only 16 out of the 517 patients in the study were from the U.S. We will show you that there are differences in the subsequent care based on region that influences the interpretation of the trial, and again, the applicability of the results to patients in the U.S…. All of this [subsequent care] was off protocol.

128. Dr. Dodd, a member of the ODAC panel and a statistical expert at the National Institute of Health, also strongly criticized the defective crossover design:

> So this is a textbook example of why we recommend against crossover. We don't know whether sorafenib worked well and

> tivozanib didn't, or whether tivozanib worked well, or whether the survival signal is just noise.
>
> I would have advised strongly against crossover, and if it was deemed absolutely necessary from an ethics perspective, then I would have recommended against allowing the one-way crossover. So this saddens me because we want to speed up the drug development process, but when a trial is poorly conducted, we get fuzzy answers.
>
> The crossover in this case and the way it was conducted -- it was one-sided going from the tivozanib, the experimental arm, or from the sorafenib arm to the tivozanib -- brings up a question for me about the integrity of the progression-free survival result.

129. Dr. Logan, a biostatistical expert on the ODAC panel, explained that the defective trial evidence presented by AVEO fell far short of the requirement for approval:

> Approval based on a single unblinded trial, which is what we have here, really needs robust and statistically compelling and internally consistent evidence of clinical benefit.
>
> What do we have? We have modest evidence of an effect on a radiologic endpoint of progression-free survival; a marginally significant p value of .04, which in the context of typical approvals, which require two studies to be significant is not statistically convincing.
>
> We have potential concerns about a couple issues related to potential bias in the progression-free survival endpoint; effective dose reductions on sorafenib, as well as potential informative censoring, as discussed by Dr. Dodd.
>
> We also have an inconsistent effect on overall survival. In general, I think, as has been alluded to in several points, we have a poor trial design for considering the impact on survival. And survival is very important safety consideration. The use of crossover, and in particular the use of this one sided crossover, really makes the overall survival results very difficult to interpret.
>
> There have been a number of hypotheses that have been proposed for why there may be this adverse impact, but these are all hypotheses.

130. Defendant Slichenmyer, in response to pointed questions from ODAC panel members, reluctantly admitted that the Company implemented the one-way crossover after TIVO-1 had commenced, without discussing with the FDA:

> Crossover was not built into the study as it was initially conceived and discussed with health authorities here, with the FDA and with CHMP. It was only after moving ahead towards implementation of the study, talking with investigators at study sites, that they said that they really wanted the study to be designed in a way so that all of their patients could have access to tivozanib.

Defendant Slichenmyer also admitted that he and AVEO had "anticipat[ed]" that the off-protocol crossover might distort overall survival. When pushed, Defendant Slichenmyer further conceded that the analyses the Company included in the NDA to attempt to attribute the higher deaths under tivozanib to this distortion were themselves "post hoc and potentially biased."

131. Dr. Motzer, the Chief Investigator hired by AVEO for the TIVO-1 trial, explained that the crossover was implemented for economic purposes, to disincentivize patients from leaving the trial if they were randomized to the sorafenib arm (which would be known because the trial was unblinded and open label):

> So the investigators were somewhat concerned, in an environment where there was multiple drugs, that patients would not go on and stay on if they received sorafenib; if they were registered to sorafenib, that they might drop out and say, I don't really feel like going to this center. I'll go elsewhere.

132. The FDA's Dr. Pazdur also rejected any notion that high enrollment rates in Central and Eastern Europe (enticed, as AVEO's Chief Investigator admitted in Paragraph 131 above by the offer of free post-study treatment as a "crossover") were somehow outside the control of the sponsor. Instead, as Dr. Pazdur explained, the sponsor can always add sites to ensure the global distribution specified in the protocol:

> DR. PAZDUR: I'll answer your question with a question. Why was this trial done only exclusively in Eastern Europe? What was the motivating factor behind it? Was it solely accrual? Were there financial reasons? I don't know. But why was the study solely done in Europe?
>
> If you're telling me that this is such a special drug that we have here that's so much better than everything else, one would think that U.S. investigators would be chomping at the bit to be studying this drug.

> So my answer to you, or my question to you, is why is the trial only being done in Eastern Europe?
>
> DR. FINGERT: I think it actually wasn't, Dr. Pazdur. It was not intentional, and it certainly was not restricted to Eastern Europe for the sponsor.
>
> DR. PAZDUR: I realize that. But on the other hand, when people see their accruals and their patterns of accrual, they can step in to increase the number of sites.

133. Dr. Fojo, a member of the ODAC panel and Program Director for Medical Oncology at the National Cancer Institute, emphasized that the PFS advantage claimed by AVEO may have been caused by materially different dose reduction rates:

> There's something in the study design that I think is concerning to me. The dose adjustment for sorafenib was quite steep. It was a 50 percent reduction, from 400 b.i.d. to 400 q.d. The dose adjustment for tivozanib was only a third, from 1.5 to 1.
>
> So if I were setting up a study, I wouldn't set up such a discrepancy between the two drugs, that I would take my comparator and reduce it by 50 percent in response to toxicity as opposed to only a third for my active agent.
>
> I'm not quite sure there wasn't a 400/200 step along the way. Certainly, I think Dr. Motzer thinks that 400 q.d. of sorafenib is not a very effective drug, so when you reduce it to that, you're actually making it such that the comparator is at a disadvantage.

Dr. Fojo noted that the dose reduction bias likely played a significant role in shaping results because "50-some-odd percent of the patients [in the sorafenib arm] had a dose reduction."

134. Citing defective trial design and conduct, and the lack of evidence explaining the cause of shortened life among tivozanib patients, all of the members of the panel but one voted against recommending approval. A doctor on the panel described his vote as follows:

> I couldn't imagine sitting down and telling a patient that I was going to put them on a drug where the critical trial showed that it would actually shorten their survival.

Similarly, another explained:

> [T]he design of the study is simply inadequate, especially given that only one phase 3 study has been conducted. And in the sponsor's own words, the single phase 3 study was a comparison of single-line therapy versus those who received two lines of therapy.
>
> ***
>
> The amount of time that the sponsor had expended in explaining away the overall survival difference would have been better spent in conducting a better-designed study. Not having done that, we are left to guess and speculate on why the overall survival is going in the wrong direction for tivozanib.

Another summarized:

> I think if this trial had been conducted in a better way in terms of the design specifically, that we might not be here.

135. As a result of the additional adverse information disclosed in the ODAC hearing, AVEO shares declined $2.61 per share to close at $2.65 per share on May 2, 2013. This drop of nearly 50% was on massive volume of over 15 million shares.

POST-CLASS PERIOD REACTION

136. Analysts and press also reacted strongly to AVEO's scientific misconduct and failure to come clean with investors. For example, in a May 6, 2013 article published in *TheStreet.com*, senior pharmaceutical correspondent Adam Feuerstein wrote:

> The committee's response was unequivocal: There is no compelling evidence, largely because AVEO conducted a flawed clinical trial.
>
> Worse, AVEO knew it had a problem well before last Thursday's FDA panel meeting. The FDA told AVEO last May that a second clinical trial should be run. AVEO ignored that advice and didn't disclose the recommendation to anyone. There's your arrogance.

137. On or about May 24, 2013, Astellas revealed that it would not fund additional clinical trials for tivozanib as a treatment for kidney cancer, and would not seek approval in Europe for tivozanib as a treatment for kidney cancer.

138. On June 11, 2013, AVEO conducted a conference call to discuss a complete response letter it had received from the FDA, rejecting its NDA for tivozanib. In the conference call, Defendants Slichenmyer and AVEO conceded they had known since May 2012 that the FDA wanted to see an additional clinical trial but had disregarded that advice:

> Since ODAC, we have received questions about FDA's recommendation for a second study. Let me walk you through our thinking on that and provide some context. Let's start with the pre-NDA meeting we had in May of 2012. At that meeting, we discussed with the agency the results from an interim analysis of overall survival, along with other efficacy and safety data.
>
> The agency expressed concern about the adverse trend in OS. Directly from the FDA's minutes from that meeting I quote, "The agency expressed a concern about the adverse trend in overall survival. Further discussion of these findings will be required at the time of filing, and if the application is filed, there will be a review issue that could affect approvability. The FDA recommended that the sponsor conduct a second adequately-powered randomized trial in a population comparable to that in the U.S." At that time, the agency requested that the NDA submission include the results from the final OS analysis, which was expected sometime after August 2012.

139. On July 3, 2013, AVEO received an investigational subpoena for documents at AVEO "concerning tivozanib" and also "including related communications with the FDA, investors and others." AVEO later admitted in an SEC filing that it had received the subpoena, but has not released the actual subpoena or its communications with the SEC regarding the investigation. The fact that a subpoena was issued alone indicates that the investigation is formal rather than informal. The SEC only issues investigational subpoenas as part of formal inquiry into potential violations of federal securities laws.

140. An August 13, 2013 article from Chris Rees that was published in *TheStreet.com* criticized Defendants for withholding the adverse information identified herein regarding their May 2012 regulatory communications with the FDA:

> In my view, this was material information that should have been fully disclosed to investors….
>
> It appears AVEO knew this OS data was a bigger issue for the FDA than what shareholders were told. It also appears that AVEO knew the possibility (or probability) of the FDA requiring a new OS trial was greater than they led investors to believe.
>
> If the information disclosed (for the first time) in [a post-Class Period conference call] had been made public prior to AVEO's ODAC meeting, investors who lost money may have decided to reduce or limit the size of their investment, or may have decided not to invest in AVEO at all.[4]

CLASS ACTION ALLEGATIONS

141. Plaintiffs bring this action as a class action pursuant to Federal Rule of Civil Procedure 23(a) and (b)(3) on behalf of all those who purchased or otherwise acquired AVEO common stock between January 3, 2012 and May 1, 2013, both dates inclusive (the "Class"); and were damaged thereby. Excluded from the Class are defendants herein, the officers and directors of the Company, at all relevant times, members of their immediate families and their legal representatives, heirs, successors or assigns and any entity in which defendants have or had a controlling interest.

142. The members of the Class are so numerous that joinder of all members is impracticable. Throughout the Class Period, AVEO securities were actively traded on the NASDAQ. While the exact number of Class members is unknown to Plaintiffs at this time and can be ascertained only through appropriate discovery, Plaintiffs believe that there are several hundred, if not thousands, of members in the proposed Class. According to the Annual Report that AVEO filed with the SEC on Form 10-K on March 11, 2013, AVEO had eighty-eight (88) record holders, which refers generally to the number of brokers that register shares on behalf of

[4] *See* Chris Rees, "AVEO: Anatomy of a trade gone wrong," *TheStreet.com*, August 13, 2013.

their clients, together with any shareholders that had specifically arranged for direct registration of shares. According to the 10-K, AVEO and its executives "believe that the number of beneficial owners of our common stock [as of February 2013] was substantially greater." Record owners and beneficial owners who may be members of the Class may be identified from records maintained by AVEO or its transfer agent and notice directed through brokers as is customarily made in securities class actions.

143. Plaintiffs' claims are typical of the claims of the members of the Class as all members of the Class are similarly affected by defendants' wrongful conduct in violation of federal law and the same misrepresentations and omissions complained of herein.

144. Plaintiffs will fairly and adequately protect the interests of the members of the Class and has retained counsel competent and experienced in class and securities litigation. Plaintiffs have no interests antagonistic to or in conflict with those of the Class.

145. Common questions of law and fact exist as to all members of the Class and predominate over any questions solely affecting individual members of the Class. Among the questions of law and fact common to the Class are:

- whether the federal securities laws were violated by Defendants' acts as alleged herein;
- whether Defendants misrepresented their regulatory communications with the FDA during the Class Period as alleged herein;
- whether Defendants concealed from investors adverse information communicated to them by the FDA regarding the FDA's concerns regarding higher risk of death for tivozanib patients in the TIVO-1 trial, and if so, whether the omitted information was material;
- whether Defendants concealed from investors adverse information communicated to them by the FDA regarding the potential impact of the higher risk of death on the approvability of tivozanib, and if so, whether the omitted information was material;
- whether Defendants concealed from investors adverse information communicated to them by the FDA regarding the FDA's request for an additional, well-controlled

clinical trial in a population comparable to the United States, and if so, whether the omitted information was material;

- whether Defendants acted knowingly or recklessly in issuing false and misleading statements identified herein;
- whether the price of AVEO's common stock was artificially inflated during the Class Period because of the Defendants' conduct complained of herein; and
- whether the members of the Class have sustained damages and, if so, what is the proper measure of damages.

146. A class action is superior to all other available methods for the fair and efficient adjudication of this controversy since joinder of all members is impracticable. Furthermore, as the damages suffered by individual Class members may be relatively small, the expense and burden of individual litigation make it impossible for members of the Class to individually redress the wrongs done to them. There will be no difficulty in the management of this action as a class action.

147. Plaintiffs will rely, in part, upon the presumption of reliance established by the fraud-on-the-market doctrine in that:

- defendants made public misrepresentations or failed to disclose material facts during the Class Period, which misrepresentations were conveyed to investors and distorted the trading price of AVEO shares during the Class Period;
- the omissions and misrepresentations were material;
- AVEO securities are traded in efficient markets;
- the Company's shares were liquid and traded with moderate to heavy volume during the Class Period;
- the Company traded on the NASDAQ, and was covered by multiple analysts;
- the misrepresentations and omissions alleged are of the type that would tend to induce a reasonable investor to misjudge the value of the Company's securities as is demonstrated by the sharp revaluation during each of the three partial disclosures alleged herein; and

- Plaintiffs and members of the Class purchased and/or sold AVEO securities between the time the defendants failed to disclose or misrepresented material facts and the time the true facts were disclosed, without knowledge of the omitted or misrepresented facts.

148. Based upon the foregoing, Plaintiffs and the members of the Class are entitled to a presumption of reliance upon the integrity of the market.

149. Plaintiffs may also rely, in part, on the presumption of reliance available for omissions under *Affiliated Ute Citizens v. United States*, 406 U.S. 128 (1972), in that the material misrepresentations alleged herein are primarily material omissions and not affirmative misrepresentations of fact.

COUNT I

(Against All Defendants For Violations of Section 10(b) And Rule 10b-5 Promulgated Thereunder)

150. Plaintiffs repeat and reallege each and every allegation contained above as if fully set forth herein.

151. This Count is asserted against all defendants and is based upon Section 10(b) of the Exchange Act, 15 U.S.C. § 78j(b), and Rule 10b-5 promulgated thereunder by the SEC.

152. During the Class Period, Defendants knowingly or recklessly misrepresented material facts and omitted to state material facts necessary in order to make the statements made, in light of the circumstances under which they were made, not misleading. Specifically, among the other misrepresentations identified in detail in the paragraphs above, Defendants: (a) misrepresented their regulatory communications with the FDA; (b) omitted material adverse information regarding study misconduct and design flaws in the TIVO-1 trial which confounded results as to both overall survival and progression-free survival, rendering the trial uninterpretable, invalid, and without any evidentiary value; (c) omitted material adverse

information regarding concerns expressed to them by the FDA regarding a higher risk of death in tivozanib, and the effect of that higher risk of death upon approvability; and (d) omitted material adverse information regarding the FDA's request, communicated to them, that AVEO conduct an additional clinical trial.

153. Pursuant to this course of conduct, each of the Individual Defendants made the material misrepresentations attributed to him and participated directly or indirectly in the dissemination of the Company's misrepresentations in quarterly and annual reports, SEC filings, press releases and investor conferences.

154. By virtue of their positions at AVEO and direct participation in the design, conduct or oversight of the tivozanib development program and clinical testing, and their participation in and/or briefing regarding regulatory communications between the Company and the FDA, Individual Defendants had actual knowledge of the materially false and misleading statements and material omissions alleged herein and either recklessly disregarded the truth or intended thereby to deceive Plaintiffs and the other members of the Class.

155. Certain information showing that Defendants acted knowingly or with reckless disregard for the truth is peculiarly within Defendants' knowledge and control. As the senior managers and/or directors of AVEO, the Individual Defendants had knowledge of the details of AVEO's regulatory communications with the FDA and clinical trial results regarding the information misrepresented herein, and to conceal wrongdoing have refused to release most of that information to investors, including the full minutes, meeting packages, and correspondence related to AVEO's December 2008, May 2009 and May 2012 meetings with the FDA, and other regulatory communications between the FDA and AVEO.

156. The Individual Defendants are liable both directly and indirectly for the wrongs complained of herein. Because of their positions of control and authority, the Individual Defendants were able to and did, directly or indirectly, control the content of the statements of AVEO. As officers and/or directors of a publicly-held company, the Individual Defendants had a duty to disseminate timely, accurate, and truthful information with respect to AVEO's businesses, operations, future financial condition and future prospects.

157. Alternately, even if Individual Defendants did not have an absolute duty to disclose the true facts alleged herein as a result of the importance of those facts to AVEO's business and prospects, each of the Individual Defendants assumed the duty to speak wholly and truthfully to investors regarding the topics on which he spoke, including AVEO's regulatory communications and clinical trials.

158. As a result of the dissemination of the aforementioned false and misleading reports, releases and public statements, the market price of AVEO securities was artificially inflated throughout the Class Period. Without benefit of the true facts misrepresented and omitted by Defendants, Plaintiffs and the other members of the Class purchased AVEO securities at artificially inflated prices and relied upon the price of the securities, the integrity of the market for the securities and/or upon statements disseminated by defendants, and were damaged thereby.

159. Had Plaintiffs and the other members of the Class known the truth, they would not have purchased said securities or would not have purchased them at the inflated prices that were paid. At the time of the purchases by Plaintiffs and the Class, the true value of AVEO securities was substantially lower than the prices paid by Plaintiffs and the other members of the Class. The market price of AVEO securities declined sharply upon public disclosure of the facts alleged herein to the injury of Plaintiffs and Class members.

160. By reason of the conduct alleged herein, each of the Defendants knowingly or recklessly violated Section 10(b) of the Exchange Act and Rule 10b-5 promulgated thereunder.

161. As a direct and proximate result of Defendants' wrongful conduct, Plaintiff and the other members of the Class suffered damages in connection with their respective purchases and sales of the Company's securities during the Class Period, upon the disclosure of the truth about the Company's regulatory communications with the FDA and the design defects and scientific misconduct in their pivotal clinical trial for tivozanib, TIVO-1.

COUNT II

(Violations of Section 20(a) of the Exchange Act Against The Individual Defendants)

162. Plaintiffs repeat and reallege each and every allegation contained in the foregoing paragraphs as if fully set forth herein.

163. During the Class Period, the Individual Defendants participated in the operation and management of AVEO, and/or directed and oversaw the operation and management of AVEO's business and regulatory affairs and investor communications. Because of their positions as AVEO's most senior executives and/or directors, together with the small size of AVEO, the importance of tivozanib and regulatory communications regarding tivozanib to AVEO, and typical industry practices of participation in FDA meetings and debriefing executives and directors regarding those meetings, each of the Individual Defendants knew the material adverse non-public information omitted from investors as described herein.

164. Each of the Individual Defendants, as a result of his role as a top executive and/or director of AVEO, had the ability to and did exercise control over AVEO and its public representations to investors and analysts. Each had the obligation to disseminate only truthful information with respect to AVEO's operations and the development and regulatory progress of

its key drug, tivozanib, and to correct promptly any public statements issued by AVEO which had become materially false or misleading. The Individual Defendants therefore, were "controlling persons" of AVEO within the meaning of Section 20(a) of the Exchange Act. In this capacity, they participated in the unlawful conduct alleged which artificially inflated the market price of AVEO securities.

165. By reason of the above conduct, the Individual Defendants are liable pursuant to Section 20(a) of the Exchange Act for the violations committed by AVEO.

166. Defendant Ha-Ngoc, by virtue of the fact that Defendants Slichenmyer and Johnston reported to him and were subordinate to him in the corporate structure of AVEO, also had the opportunity and power to control the public statements of Defendants Slichenmyer and Johnston, and was a "controlling person" of Defendants Slichenmyer and Johnston within the meaning of Section 20(a) of the Exchange Act. In this capacity, he participated in the unlawful conduct of Defendants Slichenmyer and Johnston.

167. By reason of the above conduct, Defendant Ha-Ngoc is also liable pursuant to Section 20(a) of the Exchange Act for the violations committed by Defendants Slichenmyer and Johnston.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs demand judgment against Defendants as follows:

A. Determining that the instant action may be maintained as a class action under Rule 23 of the Federal Rules of Civil Procedure, and certifying Plaintiffs as the Class representatives;

B. Requiring Defendants to pay damages sustained by Plaintiffs and the Class by reason of the acts and transactions alleged herein;

C. Awarding Plaintiffs and the other members of the Class prejudgment and post-judgment interest, as well as their reasonable attorneys' fees, expert fees and other costs; and

D. Awarding such other and further relief as this Court may deem just and proper.

DEMAND FOR TRIAL BY JURY

Plaintiffs hereby demand a trial by jury.

Dated: February 3, 2014

By their attorneys,

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CERTIFICATE OF SERVICE

I hereby certify that this document filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) on February 3, 2014.

/s/ Adam M. Stewart
Adam M. Stewart